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Patentanmeldung Nr. Patent application No. Demande de brevet n°

02293238.8

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

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AstraZeneca AB

151 85 Södertälje
SUEDE

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(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Chemical compounds

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CHEMICAL COMPOUNDS

The present invention relates to certain quinazoline derivatives for use in the treatment of certain diseases in particular to proliferative disease such as cancer and in the preparation of medicaments for use in the treatment of proliferative disease, to novel quinazoline compounds and to processes for their preparation, as well as pharmaceutical compositions containing them as active ingredient.

Cancer (and other hyperproliferative disease) is characterised by uncontrolled cellular proliferation. This loss of the normal regulation of cell proliferation often appears to occur as the result of genetic damage to cellular pathways that control progress through the cell cycle.

In eukaryotes, an ordered cascade of protein phosphorylation is thought to control the cell cycle. Several families of protein kinases that play critical roles in this cascade have now been identified. The activity of many of these kinases is increased in human tumours when compared to normal tissue. This can occur by either increased levels of expression of the protein (as a result of gene amplification for example), or by changes in expression of co activators or inhibitory proteins.

The first identified, and most widely studied of these cell cycle regulators have been the cyclin dependent kinases (or CDKs). Activity of specific CDKs at specific times is essential for both initiation and coordinated progress through the cell cycle. For example, the CDK4 protein appears to control entry into the cell cycle (the G0-G1-S transition) by phosphorylating the retinoblastoma gene product pRb. This stimulates the release of the transcription factor E2F from pRb, which then acts to increase the transcription of genes necessary for entry into S phase. The catalytic activity of CDK4 is stimulated by binding to a partner protein, Cyclin D. One of the first demonstrations of a direct link between cancer and the cell cycle was made with the observation that the Cyclin D1 gene was amplified and cyclin D protein levels increased (and hence the activity of CDK4 increased) in many human tumours (Reviewed in Sherr, 1996, Science 274: 1672-1677; Pines, 1995, Seminars in Cancer Biology 6: 63-72). Other studies (Loda et al., 1997, Nature Medicine 3(2): 231-234; Gemma et al., 1996, International Journal of Cancer 68(5): 605-11; Elledge et al. 1996, Trends in Cell Biology 6; 388-392) have shown that negative regulators of CDK function are frequently down regulated or deleted in human tumours again leading to inappropriate activation of these kinases.

More recently, protein kinases that are structurally distinct from the CDK family have been identified which play critical roles in regulating the cell cycle and which also appear to be important in oncogenesis. These include the newly identified human homologues of the *Drosophila* aurora and *S.cerevisiae* Ipl1 proteins. The three human homologues of these genes Aurora-A, Aurora-B and Aurora-C (also known as aurora2, aurora1 and aurora3 respectively) encode cell cycle regulated serine-threonine protein kinases (summarised in Adams *et al.*, 2001, Trends in Cell Biology. 11(2): 49-54). These show a peak of expression and kinase activity through G2 and mitosis. Several observations implicate the involvement of human aurora proteins in cancer. This evidence is particularly strong for Aurora-A. The Aurora-A gene maps to chromosome 20q13, a region that is frequently amplified in human tumours including both breast and colon tumours. Aurora-A may be the major target gene of this amplicon, since Aurora-A DNA is amplified and mRNA overexpressed in greater than 50% of primary human colorectal cancers. In these tumours Aurora-A protein levels appear greatly elevated compared to adjacent normal tissue. In addition, transfection of rodent fibroblasts with human Aurora-A leads to transformation, conferring the ability to grow in soft agar and form tumours in nude mice (Bischoff et al., 1998, The EMBO Journal. 17(11): 3052-3065). Other work (Zhou et al., 1998, Nature Genetics. 20(2): 189-93) has shown that artificial overexpression of Aurora-A leads to an increase in centrosome number and an increase in aneuploidy, a known event in the development of cancer. Other work has shown an increase in expression of Aurora-B (Adams *et al.*, 2001, Chromsoma. 110(2):65-74) and Aurora-C (Kimura *et al.*, 1999, Journal of Biological Chemistry, 274(11): 7334-40) in tumour cells when compared to normal cells.

Importantly, it has also been demonstrated that abrogation of Aurora-A expression and function by antisense oligonucleotide treatment of human tumour cell lines (WO 97/22702 and WO 99/37788) leads to cell cycle arrest and exerts an antiproliferative effect in these tumour cell lines. Additionally, small molecule inhibitors of Aurora-A and Aurora-B have been demonstrated to have an antiproliferative effect in human tumour cells (Keen *et al.* 2001, Poster #2455, American Association of Cancer research annual meeting). This indicates that inhibition of the function of Aurora-A (and possibly Aurora-B) will have an antiproliferative effect that may be useful in the treatment of human tumours and other hyperproliferative diseases. Further, inhibition of Aurora kinases as a therapeutic approach to these diseases may have significant advantages over targeting signalling pathways upstream of the cell cycle (e.g. those activated by growth factor receptor tyrosine kinases such as epidermal growth

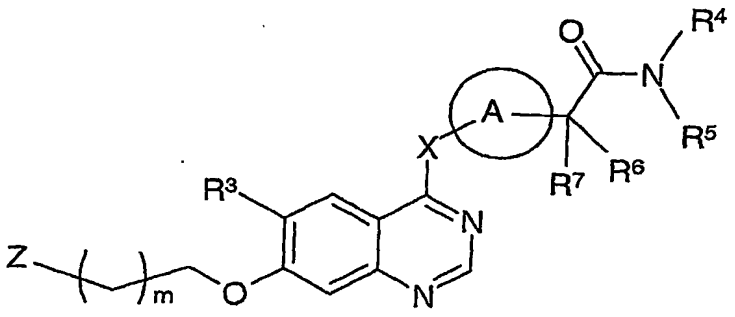
factor receptor (EGFR) or other receptors). Since the cell cycle is ultimately downstream of all of these diverse signalling events, cell cycle directed therapies such as inhibition of Aurora kinases would be predicted to be active across all proliferating tumour cells, whilst approaches directed at specific signalling molecules (e.g. EGFR) would be predicted to be active only in the subset of tumour cells which express those receptors. It is also believed that significant "cross talk" exists between these signalling pathways meaning that inhibition of one component may be compensated for by another.

A number of quinazoline derivatives have been proposed hitherto for use in the inhibition of various kinases. For example, WO 96/09294, WO 96/15118 and WO 99/06378 describe the use of certain quinazoline compounds as receptor tyrosine kinase inhibitors, which may be useful in the treatment of proliferative disease and WO 00/21955 discloses certain quinazoline derivatives as inhibitors of the effects of VEGF.

Quinazoline derivatives have also been disclosed for use in the inhibition of Aurora-A kinase. WO 02/00649 discloses quinazoline derivative bearing a 5-membered heteroaromatic ring where the ring is, in particular, substituted thiazole or substituted thiophene. However despite the compounds of WO 02/00649 there still exists the need for further compounds having Aurora kinase inhibitory properties.

The applicants have been successful in finding a novel series of compounds which inhibit the effects of the Aurora kinases and in particular Aurora-A and Aurora-B kinase and which have certain properties that make them particularly useful in formulating medicaments for the treatment of disease. In particular the compounds are of use in the treatment of proliferative disease such as cancer, in particular in diseases such as colorectal, breast or pancreatic cancer where Aurora kinases are known to be active.

According to one aspect of the present invention there is provided a compound of formula (I):



formula (I)

wherein A is 5-membered heteroaryl containing a nitrogen atom and optionally containing one or two further nitrogen atoms;

X is O, S, S(O), $S(O)_2$ or NR^{14};

m is 0, 1, 2 or 3;

Z is a group selected from $-NR^1R^2$, phosphonooxy, C_{3-6}cycloalkyl (substituted by phosphonooxy or C_{1-4}alkyl (substituted by phosphonooxy)) and a 4- to 7-membered ring linked via a carbon atom containing a nitrogen atom and optionally containing a further nitrogen atom, which ring may be saturated, partially saturated or unsaturated wherein the ring is substituted on carbon or nitrogen by phosphonooxy or C_{1-4}alkyl (substituted by phosphonooxy) and wherein the ring is optionally further substituted on carbon or nitrogen by 1, 2 or 3 halo or C_{1-4}alkyl groups;

R^1 is $-COR^8$, $-CONR^8R^9$ or C_{1-6}alkyl (substituted by phosphonooxy and optionally further substituted by 1 or 2 halo or methoxy groups);

R^2 is hydrogen, $-COR^{10}$, $-CONR^{10}R^{11}$, C_{1-6}alkyl (optionally substituted by 1, 2 or 3 halo or C_{1-4}alkoxy groups or $-S(O)_pR^{11}$ (where p is 0, 1 or 2) or phosphonooxy), C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl and C_{3-6}cycloalkylC_{1-4}alkyl;

or R^1 and R^2 together with the nitrogen to which they are attached form a 4- to 7- membered ring optionally containing a further nitrogen atom which may be saturated, partially saturated or unsaturated wherein the ring is substituted on carbon or nitrogen by a group selected from phosphonooxy and C_{1-4}alkyl (substituted by phosphonooxy or $-NR^8R^9$) and where the ring is optionally further substituted onc arbon or nitrogen by 1, 2 or 3 halo or C_{1-4}alkyl groups;

R^3 is hydrogen, halo, cyano, nitro, C_{1-6}alkoxy, C_{1-6}alkyl, $-OR^{12}$, $-CHR^{12}R^{13}$, $-OC(O)R^{12}$, $-C(O)R^{12}$, $-NR^{12}C(O)R^{13}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}SO_2R^{13}$ or $-NR^{12}R^{13}$;

R^4 is hydrogen or a group selected from C_{1-4}alkyl, heteroaryl, heteroarylC_{1-4}alkyl, aryl and arylC_{1-4}alkyl where the group is optionally substituted by 1, 2 or 3 substitutents selected from halo, methyl, ethyl, cyclopropyl and ethynyl;

R^5 is selected from hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{3-6}cycloalkyl and C_{3-6}cycloalkylC_{1-4}alkyl;

R^6 and R^7 are independently hydrogen, halo, C_{1-4}alkyl, C_{3-6}cycloalkyl, hydroxy and C_{1-4}alkoxy;

R^8 is C_{1-4}alkyl substituted by phosphonooxy and optionally further substituted by 1 or 2 halo or methoxy groups;

R^9 is hydrogen or C_{1-4}alkyl;

R^{10} is hydrogen or C_{1-4}alkyl (optionally substituted by halo, C_{1-4}alkoxy, $S(O)_q$ (where q is 0, 1 or 2) or phosphonoxy);

R^{11}, R^{12}, R^{13} and R^{14} are independently hydrogen, C_{1-4}alkyl or heterocyclyl;

or a pharmaceutically acceptable salt thereof.

Within the present invention, it is to be understood that, insofar as certain of compounds of formula (I) herein defined may exist in optically active or racemic forms by virtue of one or more asymmetric carbon or sulphur atoms, the invention includes in its definition any such optically active or racemic form which possesses aurora kinase inhibitory activity and in particular Aurora-A and/or Aurora-B kinase inhibitory activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

Within the present invention it is to be understood that a compound of formula (I) or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which has Aurora kinase inhibitory activity and in particular Aurora-A and/or Aurora-B kinase inhibitory activity and is not to be limited merely to any one tautomeric form utilised within the formulae drawings.

It is also to be understood that certain compounds of formula (I) and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which have Aurora kinase inhibitory activity and in particular Aurora-A and/or Aurora-B kinase inhibitory activity.

The present invention relates to the compounds of formula (I) as hereinbefore defined as well as to the salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula (I) and their pharmaceutically acceptable salts. Pharmaceutically acceptable salts of the invention may, for example, include acid addition salts of compounds of formula (I) as hereinbefore defined which are sufficiently basic to form such salts. Such acid addition salts include but are not limited to fumarate, methanesulphonate, hydrochloride, hydrobromide, citrate and maleate salts and salts formed with phosphoric and sulphuric acid. In addition where compounds of formula (I) are sufficiently acidic, salts are base salts and examples include but are not limited to, an alkali metal salt for example sodium or potassium,

an alkaline earth metal salt for example calcium or magnesium, or organic amine salt for example triethylamine, ethanolamine, diethanolamine, triethanolamine, morpholine, *N*-methylpiperidine, *N*-ethylpiperidine, dibenzylamine or amino acids such as lysine.

The compounds of formula (I) may also be provided as *in vivo* hydrolysable esters. An *in vivo* hydrolysable ester of a compound of formula (I) containing carboxy or hydroxy group is, for example a pharmaceutically acceptable ester which is cleaved in the human or animal body to produce the parent acid or alcohol. Such esters can be identified by administering, for example, intravenously to a test animal, the compound under test and subsequently examining the test animal's body fluid.

Suitable pharmaceutically acceptable esters for carboxy include C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

Suitable pharmaceutically-acceptable esters for hydroxy include inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α-acyloxyalkyl ethers and related compounds which as a result of the *in-vivo* hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in-vivo* hydrolysable ester forming groups for hydroxy include C_{1-10}alkanoyl, for example formyl, acetyl; benzoyl; phenylacetyl; substituted benzoyl and phenylacetyl, C_{1-10}alkoxycarbonyl (to give alkyl carbonate esters), for example ethoxycarbonyl; di-C_{1-4}alkylcarbamoyl and *N*-(di-C_{1-4}alkylaminoethyl)-*N*-C_{1-4}alkylcarbamoyl (to give carbamates); di-C_{1-4}alkylaminoacetyl and carboxyacetyl. Examples of ring substituents on phenylacetyl and benzoyl include aminomethyl, C_{1-4}alkylaminomethyl and di-(C_{1-4}alkyl)aminomethyl, and morpholino or piperazino linked from a ring nitrogen atom via a methylene linking group to the 3- or 4- position of the benzoyl ring. Other interesting *in vivo* hydrolysable esters include, for example, $R^A C(O)OC_{1-6}$alkyl-CO-, wherein R^A is for example, benzyloxy-C_{1-4}alkyl, or phenyl). Suitable substituents on a phenyl group in such esters include, for example, 4-C_{1-4}piperazino-C_{1-4}alkyl, piperazino-C_{1-4}alkyl and morpholino-C_{1-4}alkyl.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight chain version only and references to individual branched-chain alkyl groups such as "*tert*-butyl" are specific for the branched chain version only. An analogous convention applies to other generic terms, for example "alkenyl" and "alkynyl".

"Cycloalkyl" is a monocyclic, saturated alkyl ring and "aryl" is monocyclic or bicyclic.

Unless otherwise specified "heteroaryl" is a monocyclic or bicyclic aromatic ring containing 5 to 10 ring atoms of which 1, 2, 3 or 4 ring atoms are chosen from nitrogen, sulphur or oxygen where a ring nitrogen or sulphur may be oxidised.

"Heterocyclyl" is a saturated, partially saturated or unsaturated, monocyclic or bicyclic ring containing 4 to 12 atoms of which 1, 2, 3 or 4 ring atoms are chosen from nitrogen, sulphur or oxygen, which may be carbon or nitrogen linked, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-; wherein a ring nitrogen or sulphur atom is optionally oxidised to form the N-oxide or S-oxide(s); wherein a ring –NH is optionally substituted by acetyl, formyl, methyl or mesyl; and wherein a ring is optionally substituted by one or more halo.

"Phosphonooxy" is in one aspect a group of formula $-OP(O)(OH)_2$. However the term "phosphonooxy" also includes salts such as those formed with alkali metal ions such as sodium or potassium ions or alkaline earth metal ions, for example calcium or magnesium ions.

Where optional substituents are chosen from "1 or 2", from "1, 2, or 3" or from "1, 2, 3 or 4" groups or substituents it is to be understood that this definition includes all substituents being chosen from one of the specified groups i.e. all substitutents being the same or the substituents being chosen from two or more of the specified groups i.e. the substitutents not being the same.

Compounds of the present invention have been named with the aid of computer software (ACD/Name version 6.6 or ACD Name Batch version 6.0).

Suitable values for any R group (R^1 to R^{14}) or any part or substitutent for such groups include:

for C_{1-4}alkyl:	methyl, ethyl, propyl, isopropyl, butyl, 2-methylpropyl and *tert*-butyl;
for C_{1-6}alkyl:	C_{1-4}alkyl, pentyl, 2,2-dimethylpropyl, 3-methylbutyl and hexyl;
for C_{2-4}alkenyl:	vinyl, allyl and 1-propenyl;

for C_{2-6}alkenyl: C_{2-4}alkenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methylbut-2-enyl, 3-methylbut-1-enyl, 1-pentenyl, 3-pentenyl and 4-hexenyl;

for C_{2-4}alkynyl: ethynyl, 1-propynyl, 2-propynyl and 3-butynyl;

for C_{2-6}alkynyl: C_{2-4}alkynyl, 2-pentynyl, hexynyl and 1-methylpent-2-ynyl;

for C_{3-6}cycloalkyl: cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl;

for C_{3-6}cycloalkylC_{1-4}alkyl: cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexylmethyl;

for aryl: phenyl and naphthyl;

for arylC_{1-4}alkyl: benzyl, phenethyl, naphthylmethyl and naphthylethyl;

for halo: fluoro, chloro, bromo and iodo;

for C_{1-4}alkoxy: methoxy, ethoxy, propoxy and isopropoxy;

for C_{1-6}alkoxy: C_{1-4}alkoxy, pentyloxy, 1-ethylpropoxy and hexyloxy;

for heteroaryl: pyridyl, imidazolyl, quinolinyl, cinnolyl, pyrimidinyl, thiophenyl, pyrrolyl, pyrazolyl, thiazolyl, triazolyl, oxazolyl, isoxazolyl and pyrazinyl and preferably thiazolyl, pyridyl, imidazolyl and pyrimidinyl;

for heteroarylC_{1-4}alkyl: pyridylmethyl, pyridylethyl, pyrimidinylethyl, pyrimidinylpropyl, pyrimidinylbutyl, imidazolylpropyl, imidazolylbutyl, quinolinylpropyl, 1,3,4-triazolylpropyl and oxazolylmethyl;

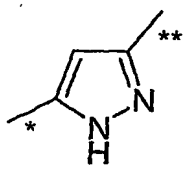
for heterocyclyl: furyl, thienyl, pyrrolyl, pyrrolidinyl, imidazolyl, triazolyl, thiazolyl, tetrazolyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, quinolinyl, isoquinolinyl, quinoxalinyl, benzothiazolyl, benzoxazolyl, benzothienyl, benzofuryl, piperidinyl, *N*-acetylpiperidinyl, *N*-methylpiperidinyl, *N*-formylpiperazinyl, *N*-mesylpiperazinyl, homopiperazinyl, piperazinyl, azetidinyl, oxetanyl, morpholinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, indolinyl, pyranyl, dihydro-*2H*-pyranyl, tetrahydrofuranyl, 2,5-dioximidazolidinyl, 2,2-dimethyl-1,3-dioxolanyl and 3,4-dimethylenedioxybenzyl.

It should be noted that examples given for terms used in the description are not limiting.

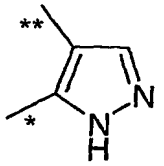
Preferred values of A, X, m, Z, R^3, R^4, R^5, R^6 and R^7 are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined

hereinbefore or hereinafter.

In one aspect of the invention A is pyrrolyl, pyrazolyl, imidazolyl or triazolyl. In a further aspect A is a group of formula (a), (b), (c), (d) or (e):



(a)



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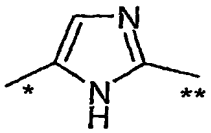
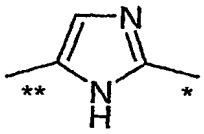
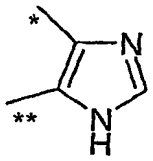


(c)



(d)



(e)

where * is the point of attachment to the X group of formula (I) and ** is the point of attachment to the (CR^6R^7) group of formula (I). In a preferred aspect A is pyrazolyl. In a more preferred aspect A is a group of formula (a) as defined above.

In one aspect of the invention X is NR^{14}, O or S. In another aspect X is NR^{14}. In yet another aspect X is NH.

In one aspect of the invention m is 1 or 2. In another aspect m is 1. In a further aspect m is 2.

In one aspect of the invention Z is $-NR^1R^2$.

In one aspect of the invention R^1 is C_{1-5}alkyl substituted by phosphonooxy. In another aspect R^1 is C_{1-5}alkyl substituted by phosphonooxy and further substituted by 1 or 2 halo. In a further aspect R^1 is 2-phosphonooxyethyl, 2-phosphonooxy-1,1-dimethylethyl, 2-phosphonooxy-2-methylethyl, 3-phosphonooxy-1,1-dimethylpropyl, 3-phosphonooxypropyl and 4-phosphonooxybutyl. In yet another aspect R^1 is 2-phosphonooxyethyl.

In one aspect of the invention R^2 is hydrogen, C_{1-6}alkyl (optionally substituted by 1, 2 or 3 halo or C_{1-4}alkoxy groups), C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl and C_{3-6}cycloalkylC_{1-4}alkyl. In another aspect R^2 is hydrogen, allyl, 2-propynyl, methyl, ethyl, propyl, isopropyl, 2-methylpropyl, butyl, 2,2-dimethylpropyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, 3,3,3-trifluoropropyl and 2-methoxyethyl.

In one aspect of the invention R^1 and R^2 together with the nitrogen to which they are attached form a saturated 5- to 6-membered ring optionally containing a further nitrogen atom wherein the ring is substituted on carbon or nitrogen by a group selected from phosphonooxy and C_{1-4}alkyl (substituted by phosphonooxy or $-NR^8R^9$) and where the ring is optionally further substituted on carbon or nitrogen by 1 or 2 C_{1-4}alkyl groups. In another aspect of the invention R^1 and R^2 together with the nitrogen to which they are attached form a piperidine, pyrrolidine or piperazine ring which is substituted by a group selected from phosphonooxy, phosphonooxymethyl, 2-phosphonooxyethyl and *N*-ethyl-*N*-(2-phosphonooxyethyl)aminomethyl and *N*-(2-phosphonooxyethyl)aminomethyl and where the ring is optionally further substituted by 1 or 2 methyl. In a further aspect of the invention R^1 and R^2 together with the nitrogen to which they are attached form 4-(phosphonooxymethyl)piperidinyl, 2-(phosphonooxymethyl)pyrrolidinyl, 4-(2-phosphonooxyethyl)piperazinyl, 3-(phosphonooxy)pyrrolidinyl, 3-(phosphonooxy)piperidinyl, 2-[*N*-ethyl-*N*-(2-phosphonooxyethyl)aminomethyl]pyrrolidinyl, 4-(phosphonooxy)piperidinyl, 2-[*N*-(2-phosphonooxyethyl)aminomethyl]pyrrolidinyl, 4-(2-phosphonooxyethyl)piperidinyl, 2-(2-phosphonooxyethyl)pyrrolidinyl and 2-(2-phosphonooxyethyl)piperidinyl. In yet another aspect R^1 and R^2 together with the nitrogen to which they are attached form 4-(phosphonooxymethyl)piperidinyl, 2-(phosphonooxymethyl)pyrrolidinyl and 3-(phosphonooxy)piperidinyl.

In one aspect of the invention R^3 is C_{1-4}alkoxy or hydrogen. In another aspect R^3 is methoxy.. In another aspect R^3 is hydrogen.

In one aspect R^4 is phenyl optionally substituted by 1 or 2 of fluoro or chloro. In another aspect R^4 is 3-fluorophenyl, 3-chlorophenyl, 3,5-difluorophenyl, 3,4-difluorophenyl, 2-fluorophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl and 2,5-difluorophenyl. In a further aspect R^4 is 3-fluorophenyl, 3,5-difluorophenyl and 2,3-difluorophenyl.

In one aspect R^5 is hydrogen or methyl.

In one aspect of the invention R^6 is hydrogen, fluoro, chloro or methyl. In another aspect R^6 is hydrogen.

In one aspect of the invention R^7 is hydrogen, fluoro, chloro or methyl. In another aspect R^7 is hydrogen.

In one aspect R^8 is 2-phosphonooxyethyl.

In one aspect of the invention R^9 is hydrogen, methyl or ethyl.

In one aspect of the invention R^{10} is hydrogen, methyl or ethyl.

In one aspect of the invention R^{11} is hydrogen, methyl or ethyl.

In one aspect of the invention R^{12} is hydrogen or methyl.

In one aspect of the invention R^{13} is hydrogen or methyl.

In one aspect of the invention R^{14} is hydrogen or methyl.

A preferred class of compounds is of formula (I) wherein:

A is a group of formula (a), (b), (c), (d) or (e) as defined above;

X is NH;

m is 1 or 2;

Z is $-NR^1R^2$;

R^1 is C_{1-5}alkyl substituted by phosphonooxy;

R^2 is hydrogen, C_{1-6}alkyl (optionally substituted by 1, 2 or 3 halo or C_{1-4}alkoxy groups), C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl and C_{3-6}cycloalkylC_{1-4}alkyl;

R^3 is C_{1-4}alkoxy or hydrogen;

R^4 is phenyl optionally substituted by 1 or 2 of fluoro or chloro;

R^5 is hydrogen or methyl; and

R^6 and R^7 are independently hydrogen, fluoro, chloro or methyl;

or a pharmaceutically acceptable salt thereof.

Another preferred class of compounds is of formula (I) wherein:

A is a group of formula (a) as defined above;

X is NH;

m is 1 or 2;

Z is $-NR^1R^2$;

R^1 is C_{1-5}alkyl substituted by phosphonooxy;

R^2 is hydrogen, C_{1-6}alkyl (optionally substituted by 1, 2 or 3 halo or C_{1-4}alkoxy groups), C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl and C_{3-6}cycloalkylC_{1-4}alkyl;

R^3 is C_{1-4}alkoxy or hydrogen;

R^4 is phenyl optionally substituted by 1 or 2 of fluoro or chloro;

R^5 is hydrogen or methyl; and

R^6 and R^7 are independently hydrogen, fluoro, chloro or methyl;

or a pharmaceutically acceptable salt thereof.

Another preferred class of compounds is of formula (I) wherein:

A is a group of formula (a), (b), (c), (d) or (e) as defined above;

X is NH;

m is 1 or 2;

Z is $-NR^1R^2$

R^1 and R^2 together with the nitrogen to which they are attached form a saturated 5- to 6-membered ring optionally containing a further nitrogen atom wherein the ring is substituted by a group selected from phosphonooxy and C_{1-4}alkyl (substituted by phosphonooxy or $-NR^8R^9$) and where the ring is optionally further substituted by 1 or 2 C_{1-4}alkyl groups;

R^4 is phenyl optionally substituted by 1 or 2 of fluoro or chloro;

R^5 is hydrogen or methyl; and

R^6 and R^7 are independently hydrogen, fluoro, chloro or methyl;

R^8 is 2-phosphonooxyethyl; and

R^9 is hydrogen, methyl or ethyl;

or a pharmaceutically acceptable salt thereof.

A further preferred class of compounds is of formula (I) wherein:

A is a group of formula (a) as defined above;

X is NH;

m is 1 or 2;

Z is $-NR^1R^2$

R^1 and R^2 together with the nitrogen to which they are attached form a saturated 5- to 6-membered ring optionally containing a further nitrogen atom wherein the ring is substituted on carbon or nitrogen by a group selected from phosphonooxy and C_{1-4}alkyl (substituted by phosphonooxy or $-NR^8R^9$) and where the ring is optionally further substituted on carbon or nitrogen by 1 or 2 C_{1-4}alkyl groups;

R^4 is phenyl optionally substituted by 1 or 2 of fluoro or chloro;

R^5 is hydrogen or methyl; and

R^6 and R^7 are independently hydrogen, fluoro, chloro or methyl;

R^8 is 2-phosphonooxyethyl; and

R^9 is hydrogen, methyl or ethyl;

or a pharmaceutically acceptable salt thereof.

In another aspect of the invention, preferred compounds of the invention are any one of:

{1-[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]piperidin-4-yl}methyl dihydrogen phosphate;

2-[[3-({4-[(5-{2-[(3,5-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](ethyl)amino]ethyl dihydrogen phosphate;

{(2*S*)-1-[3-({4-[(5-{2-[(3,5-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

{(2*R*)-1-[3-({4-[(5-{2-[(3,5-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

{(2*S*)-1-[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

2-[[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](propyl)amino]ethyl dihydrogen phosphate;

2-[[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](isobutyl)amino]ethyl dihydrogen phosphate;

2-[[3-({4-[(5-{2-[(3,5-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](isobutyl)amino]ethyl dihydrogen phosphate;

2-[[3-({4-[(5-{2-[(3,5-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](propyl)amino]ethyl dihydrogen phosphate;

2-[[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](isobutyl)amino]ethyl dihydrogen phosphate;

2-{(2,2-dimethylpropyl)[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate;

1-[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]piperidin-3-yl dihydrogen phosphate;

{(2*R*)-1-[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

2-[[3-({4-[(5-{2-[(3,5-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](prop-2-yn-1-yl)amino]ethyl dihydrogen phosphate;

2-[[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](isopropyl)amino]ethyl dihydrogen phosphate;

2-[[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](prop-2-yn-1-yl)amino]ethyl dihydrogen phosphate;

2-[[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](2-methoxyethyl)amino]ethyl dihydrogen phosphate;

2-{[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate;

2-{(cyclobutylmethyl)[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate;

2-[[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](3,3,3-trifluoropropyl)amino]ethyl dihydrogen phosphate;

2-{allyl[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate;

2-{cyclobutyl[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate;

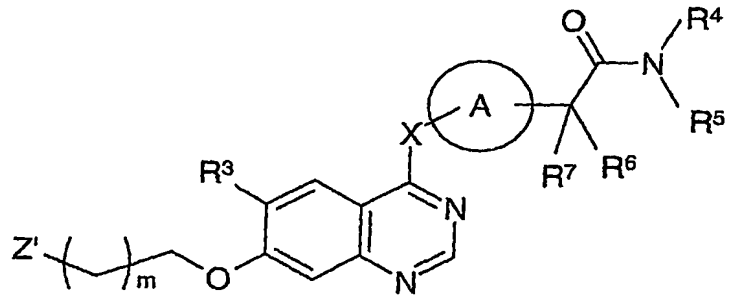
2-{cyclopentyl[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate;

2-{cyclopropyl[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate;

2-{(cyclopropylmethyl)[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate and

2-{cyclobutyl[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate.

In another aspect the present invention provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises converting a compound of formula (II) into a compound of formula (I) by phosphorylation of an appropriate hydroxy group:



formula (II)

where A, X, m, R^2, R^3, R^4, R^5, R^6, R^7 and R^9 are as defined for formula (I); and Z' is a group selected from $-NR^{1'}R^2$, hydroxy, C_{3-6}cycloalkyl (substituted by hydroxy or C_{1-4}alkyl

(substituted by hydroxy)) and a 4- to 7-membered ring linked via a carbon atom containing a nitrogen atom and optionally containing a further nitrogen atom, which ring may be saturated, partially saturated or unsaturated wherein the ring is substituted on carbon or nitrogen by hydroxy or C_{1-4}alkyl (substituted by hydroxy) and wherein the ring is optionally further substituted on carbon or nitrogen by 1, 2 or 3 halo or C_{1-4}alkyl groups; $R^{1'}$ is $-COR^{8'}$, $-CONR^{8'}R^{9}$ or C_{1-6}alkyl (substituted by hydroxy and optionally further substituted by 1 or 2 halo or methoxy groups); or $R^{1'}$ and R^{2} together with the nitrogen to which they are attached form a 4- to 7- membered ring optionally containing a further nitrogen atom which may be saturated, partially saturated or unsaturated wherein the ring is substituted onc arbon or nitrogen by a group selected from hydroxy and C_{1-4}alkyl (substituted by hydroxy or $-NR^{8'}R^{9}$) and where the ring is optionally further substituted on carbon or nitrogen by 1, 2 or 3 halo or C_{1-4}alkyl groups; and where $R^{8'}$ is C_{1-4}alkyl substituted by hydroxy and optionally further substituted by 1 or 2 halo or methoxy groups:

and thereafter if necessary:

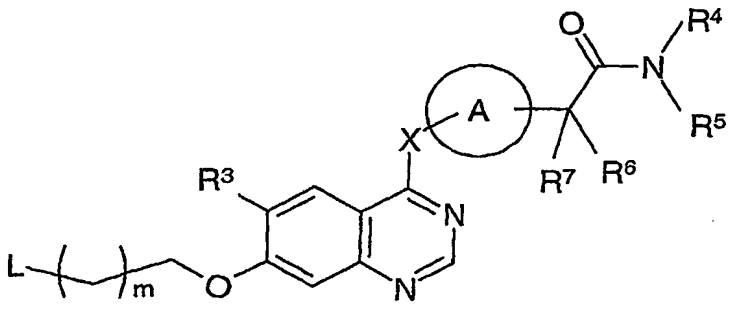
i) converting a compound of the formula (I) into another compound of the formula (I);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt.

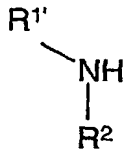
Phosphorylation may be suitably performed by treatment with 1-H tetrazole (or a suitable replacement such as S-ethyl tetrazole or pyridinium hydrochloride) and di-*tert*-butyldiethylphosphoramidite at 5 to 35 °C under an inert atmosphere for 30 minutes to 4 hours followed by treatment with an oxidizing agent such as meta-chloroperbenzoic acid (mCPBA) or 30% aqueous hydrogen peroxide at -10 to 25 °C for 2 to 18 hour. Deprotection of the *tert*-butyl groups to yield the phosphate group is required as a final step with these reagents and may be readily achieved by treatment with 4.0 N hydrochloric acid in 1,4-dioxane at 10 to 35 °C for 12 to 18 hours.

This process may further comprise a method for the preparation of a compound of formula (II) where Z' is $-NR^{1'}R^{2}$ which method comprises the reaction of a compound of formula (III) where L is a leaving group such as halo (e.g.chloro):



formula (III)

with an amine of formula (IV):

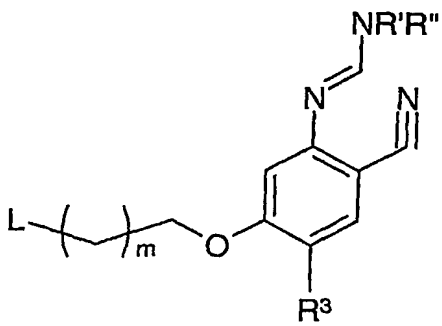


formula (IV).

Suitable reaction conditions for this process include heating a compound of formula (III) with an excess of amine of formula (IV) in an inert solvent such as dimethylacetamide, with or without the addition of a suitable catalyst (such as *tetra*-n-butylammoniuim iodide or potassium iodide) at a temperature of 50 to 100 °C for 12 to 72 hours. In an alternative procedure, the leaving group L in formula (III) may be a carboxaldehyde and the reaction with amine (IV) may be carried out under reductive conditions using a reducing agent such as sodium cyanoborohydride.

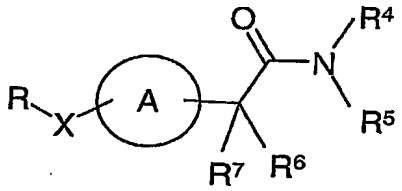
The amines of formula (IV) are known in the art or may be prepared by the skilled person using methods known in the art.

The process may further comprise a method for the preparation of a compound of formula (III) where X is NR^{14} which method comprises the reaction of a compound of formula (V) where R' and R" are alkyl groups such as methyl and ethyl and L is as defined in relation to formula (III):



formula (V)

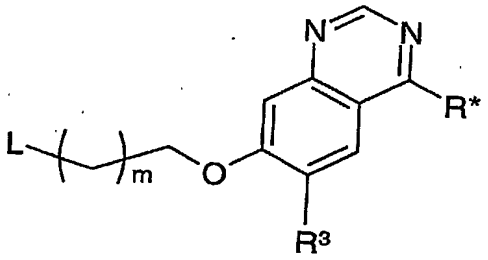
with a compound of formula (VI) where R may be either hydrogen or a group such as *tert*-butoxycarbonyl (Boc) or trityl:



formula (VI)

Such a reaction can be achieved under a range of conditions described in the literature and such as heating a compound of formula (V) with a compound of formula (VI) in a solvent such as acetic acid at a temperature of 100 to 130 °C for 2 to 18 hours.

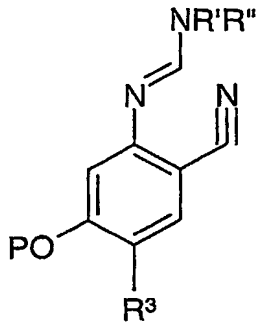
Alternatively, the process may further comprise a method for the preparation of a compound of formula (III) where X is NR^{14}, O or S which method comprises the reaction of a compound of formula (VII) where R* is a leaving group such as halo (e.g.chloro):



formula (VII)

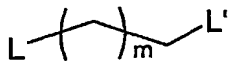
with a compound of formula (VI) where R is either hydrogen or tert-butoxycarbonyl (Boc) or trityl. Such a reaction can be achieved under a range of conditions described in the literature such as heating a compound of formula (VII) with a compound of formula (VI) in a solvent such as isopropanol or dimethylacetamide, in the presence of an acid catalyst such as hydrochloric acid, at a temperature of 80 to 100 °C for 2 to 6 hours. Alternatively the reaction may be effected using a base such as sodium hydride; carrying out the reaction in an inert solvent such as dimethylformamide at a temperature of 50 to 80 °C for 2 to 6 hours.

Compounds of formula (V) can be prepared from a compound of formula (VIII) where P is a hydroxy protecting group such as benzyl:



formula (VIII)

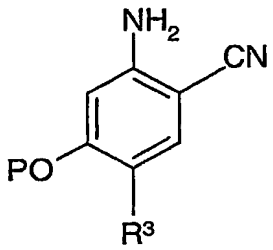
by reaction with a compound of formula (IX) where L' is a leaving group such as halo (e.g. bromo) and L is as defined in relation to formula (III):



formula (IX)

Such a reaction can be achieved (after removal of the protecting group using a method selected from those already described in the literature) under a range of conditions described in the literature such as heating a compound of formula (VIII) with a compound of formula (IX) in the presence of a catalyst such as caesium carbonate in a solvent such as acetonitrile at a temperature of 80 to 100 °C for 1 to 4 hours.

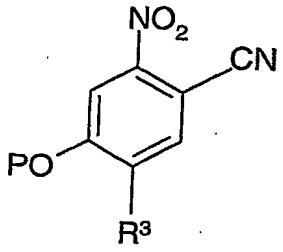
A method for the preparation of a compound of formula (VIII) comprises the reaction of a compound of formula (X) where P is as defined in relation for formula (VIII):



formula (X)

with an appropriate acetal such as *N,N*-dimethylformamide dimethyl acetal. The reaction is suitably effected in an organic solvent such as toluene or benzene, at elevated temperature, conveniently at the reflux temperature of the solvent.

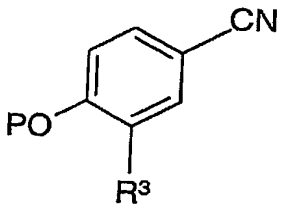
Compounds of formula (X) are either known compounds or they can be prepared by conventional methods. In particular, compounds of formula (X) may be prepared by reduction of the corresponding nitro compound of formula (XI) where P is as described in relation to formula (VIII):



formula (XI)

Suitable reaction conditions are illustrated hereinafter.

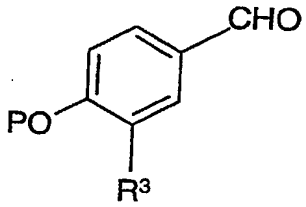
Compounds of formula (XI) may be obtained by nitration of a compound of formula (XII) where P is as defined in relation to formula (XII)



formula (XII)

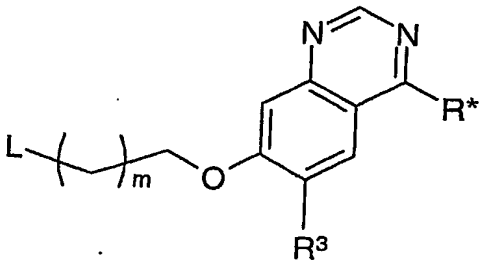
for example, using nitric acid as the nitrating agent. Again, suitable reaction conditions are illustrated hereinafter.

The nitrile of formula (XII) may be derived by reaction of the corresponding aldehyde of formula (XIII) with hydroxylamine as illustrated hereinafter:



formula (XIII)

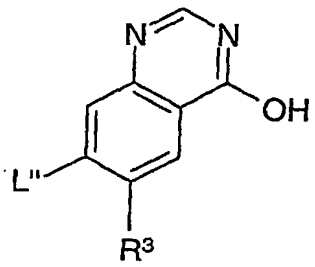
The process may further comprise a method for the preparation of a compound according to formula (VII) which method comprises the reaction of a compound of formula (XIV)



formula (XIV)

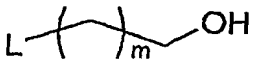
where L is a hydroxy group, with a suitable chlorinating agent such as thionyl chloride, phoshoryl chloride or phoshorus pentachloride. Again, suitable reaction conditions are illustrated hereinafter.

Compounds of formula (XIV) are either known compounds or they can be prepared by conventional methods. In particular, compounds of formula (XIV) may be prepared by reaction of a compound of formula (XV) where L'' is a leaving group such as halo (fluoro)



formula (XV)

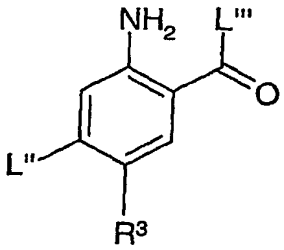
with a compound of formula (XVI) where L is a hydroxy group:



formula (XVI)

Suitable reaction conditions are illustrated hereinafter.

Compounds of formula (XV) are either known compounds or they can be prepared by conventional methods. In particular, compounds of formula (XV) may be prepared by reaction of a compound of formula (XVII) (where L'' is a leaving group such as halo (fluoro) and L''' is an alkoxy or hydroxy group) by reaction with neat formamide at a temperature of 140 to 200 °C for 3 to 6 hours.

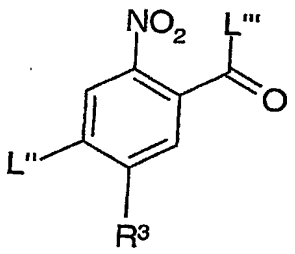


formula (XVII)

Suitable reaction conditions are illustrated hereinafter.

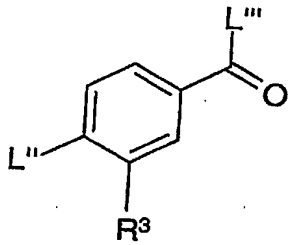
Compounds of formula (XVII) are either known compounds or they can be prepared by conventional methods. In particular, compounds of formula (XVII) may be prepared by reduction of a compound of formula (XVIII) (where L'' is a leaving group such as halo

(fluoro) and L''' is an alkoxy or hydroxy group) using a reducing agent such as sodium dithionite in a water : dichloromethane solvent system at ambient temperature for 1 to 3 hours.



formula (XVIII)

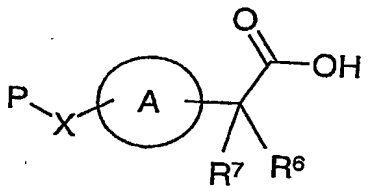
Compounds of formula (XVIII) may be obtained by nitration of a compound of formula (XIX) where L" and L''' are as defined in relation to formula (XVIII)



formula (XIX)

for example, using nitric acid as the nitrating agent. Again, suitable reaction conditions are illustrated hereinafter.

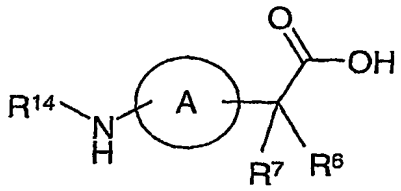
The process may further comprise a method for the preparation of a compound according to formula (VI) where X is NR^{14}, O or S which method comprises the reaction of a compound of formula (XX), where P is a suitable protecting group:



formula (XX)

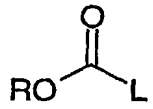
with an amine of formula HNR^4R^5 in the presence of a coupling reagent (such as O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate) and diisopropylethylamine in a solvent (such as dimethylacetamide) under inert and anhydrous conditions.

A compound of formula (XX) where X is NR^{14} and P is COOR may be prepared from a compound of formula (XXI):



formula (XXI)

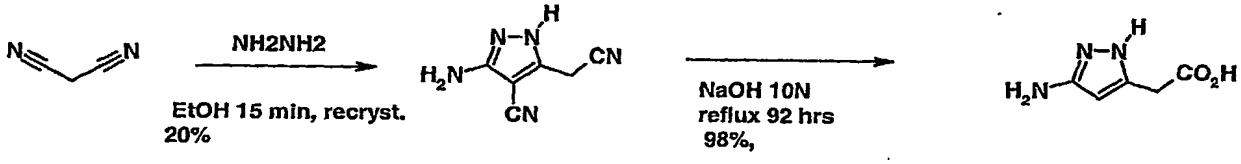
with a compound of formula (XXII) where L is an appropriate leaving group:



formula (XXII)

Suitable reagent and reaction conditions for this reaction include the use of di(*tert*-butyl)dicarbonate and triethylamine in tetrahydrofuran at 0 °C under a nitrogen atmosphere.

Compounds of formula (XXI) which comprise a heteraromatic ring are made according to the literature. However for illustrative purpose, when A is a pyrazole ring, a compound of formula (XXI) may be prepared according to the following scheme:



It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogen group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic

hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *tert*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in association with a pharmaceutically acceptable diluent or carrier.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Therefore in a further aspect of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in therapy.

Further provided is a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use as a medicament.

Additionally a compound of formula (I), or a pharmaceutically acceptable salt thereof is provided for use in a method of treatment of a warm-blooded animal such as man by therapy.

In another aspect of the invention, there is provided the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the

treatment of a disease where the inhibition of one or more Aurora kinase is beneficial. In particular it is envisaged that inhibition of Aurora-A kinase and/or Aurora-B kinase may be beneficial.

In another aspect of the invention, there is provided the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of hyperproliferative diseases such as cancer and in particular colorectal, breast or pancreatic cancer where Aurora-A is upregulated.

According to yet another aspect, there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in the method of treating a human suffering from a disease in which the inhibition of one or more Aurora kinases is beneficial, comprising the steps of administering to a person in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof. In particular it is envisaged that inhibition of Aurora-A kinase and/or Aurora-B kinase may be beneficial.

Further provided is a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in the method of treating a human suffering from a hyperproliferative disease such as cancer and in particular colorectal, breast or pancreatic cancer where Aurora-A is upregulated, comprising the steps of administering to a person in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

For the above mentioned therapeutic uses the dose administered will vary with the compound employed, the mode of administration, the treatment desired, the disorder indicated and the age and sex of the animal or patient. The size of the dose would thus be calculated according to well known principles of medicine.

In using a compound of formula (I) for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.05 mg/kg to 50 mg/kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.05 mg/kg to 25 mg/kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.05 mg/kg to 25 mg/kg body weight will be used.

The treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or

chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents :-

(i) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside and hydroxyurea; antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and iodoxyfene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5α-reductase such as finasteride;

(iii) Agents which inhibit cancer cell invasion (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);

(iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies (for example the anti-erbb2 antibody trastuzumab [Herceptin™] and the anti-erbb1 antibody cetuximab [C225]) , farnesyl transferase inhibitors, tyrosine kinase inhibitors and serine-threonine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-*N*-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), for example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, (for example the anti-vascular endothelial cell growth factor antibody

bevacizumab [Avastin™], compounds such as those disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354) and compounds that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function and angiostatin);

(vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO00/40529, WO 00/41669, WO01/92224, WO02/04434 and WO02/08213;

(vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

(viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

(ix) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the compounds of this invention within the dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

In addition to their use in therapeutic medicine, the compounds of formula (I) and their pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of cell cycle activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

The compounds of the invention inhibit the serine-threonine kinase activity of the Aurora kinases, in particular Aurora-A and/or Aurora-B and thus inhibit the cell cycle and cell proliferation. These properties may be assessed for example, using one or more of the procedures set out below.

(a) In Vitro Aurora-A kinase inhibition test

This assay determines the ability of a test compound to inhibit serine-threonine kinase activity. DNA encoding Aurora-A may be obtained by total gene synthesis or by cloning. This DNA may then be expressed in a suitable expression system to obtain polypeptide with serine-threonine kinase activity. In the case of Aurora-A, the coding sequence was isolated from cDNA by polymerase chain reaction (PCR) and cloned into the BamH1 and Not1 restriction endonuclease sites of the baculovirus expression vector pFastBac HTc (GibcoBRL/Life technologies). The 5' PCR primer contained a recognition sequence for the restriction endonuclease BamH1 5' to the Aurora-A coding sequence. This allowed the insertion of the Aurora-A gene in frame with the 6 histidine residues, spacer region and rTEV protease cleavage site encoded by the pFastBac HTc vector. The 3' PCR primer replaced the Aurora-A stop codon with additional coding sequence followed by a stop codon and a recognition sequence for the restriction endonuclease Not1. This additional coding sequence (5' TAC CCA TAC GAT GTT CCA GAT TAC GCT TCT TAA 3') encoded for the polypeptide sequence YPYDVPDYAS. This sequence, derived from the influenza hemagglutin protein, is frequently used as a tag epitope sequence that can be identified using specific monoclonal antibodies. The recombinant pFastBac vector therefore encoded for an N-terminally 6 his tagged, C terminally influenza hemagglutin epitope tagged Aurora-A protein. Details of the methods for the assembly of recombinant DNA molecules can be found in standard texts, for example Sambrook et al. 1989, Molecular Cloning - A Laboratory Manual, 2nd Edition, Cold Spring Harbor Laboratory press and Ausubel et al. 1999, Current Protocols in Molecular Biology, John Wiley and Sons Inc.

Production of recombinant virus can be performed following manufacturer's protocol from GibcoBRL. Briefly, the pFastBac-1 vector carrying the Aurora-A gene was transformed into E. coli DH10Bac cells containing the baculovirus genome (bacmid DNA) and via a transposition event in the cells, a region of the pFastBac vector containing gentamycin resistance gene and the Aurora-A gene including the baculovirus polyhedrin promoter was transposed directly into the bacmid DNA. By selection on gentamycin, kanamycin,

tetracycline and X-gal, resultant white colonies should contain recombinant bacmid DNA encoding Aurora-A. Bacmid DNA was extracted from a small scale culture of several BH10Bac white colonies and transfected into Spodoptera frugiperda Sf21 cells grown in TC100 medium (GibcoBRL) containing 10% serum using CellFECTIN reagent (GibcoBRL) following manufacturer's instructions. Virus particles were harvested by collecting cell culture medium 72 hrs post transfection. 0.5 mls of medium was used to infect 100 ml suspension culture of Sf21s containing 1 x 10^7 cells/ml. Cell culture medium was harvested 48 hrs post infection and virus titre determined using a standard plaque assay procedure. Virus stocks were used to infect Sf9 and "High 5" cells at a multiplicity of infection (MOI) of 3 to ascertain expression of recombinant Aurora-A protein.

For the large scale expression of Aurora-A kinase activity, Sf21 insect cells were grown at 28°C in TC100 medium supplemented with 10% foetal calf serum (Viralex) and 0.2% F68 Pluronic (Sigma) on a Wheaton roller rig at 3 r.p.m. When the cell density reached $1.2x10^6$ cells ml^{-1} they were infected with plaque-pure Aurora-A recombinant virus at a multiplicity of infection of 1 and harvested 48 hours later. All subsequent purification steps were performed at 4°C. Frozen insect cell pellets containing a total of 2.0 x 10^8 cells were thawed and diluted with lysis buffer (25 mM HEPES (N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulphonic acid]) pH7.4 at 4°C , 100 mM KCl, 25 mM NaF, 1 mM Na_3VO_4, 1 mM PMSF (phenylmethylsulphonyl fluoride), 2 mM 2-mercaptoethanol, 2 mM imidazole, 1 μg/ml aprotinin, 1 μg/ml pepstatin, 1 μg/ml leupeptin), using 1.0 ml per 3 x 10^7 cells. Lysis was achieved using a dounce homogeniser, following which the lysate was centrifuged at 41,000*g* for 35 minutes. Aspirated supernatant was pumped onto a 5 mm diameter chromatography column containing 500 μl Ni NTA (nitrilo-tri-acetic acid) agarose (Qiagen, product no. 30250) which had been equilibrated in lysis buffer. A baseline level of UV absorbance for the eluent was reached after washing the column with 12 ml of lysis buffer followed by 7 ml of wash buffer (25 mM HEPES pH7.4 at 4°C , 100 mM KCl, 20 mM imidazole, 2 mM 2-mercaptoethanol). Bound Aurora-A protein was eluted from the column using elution buffer (25 mM HEPES pH7.4 at 4°C , 100 mM KCl, 400 mM imidazole, 2 mM 2-mercaptoethanol). An elution fraction (2.5 ml) corresponding to the peak in UV absorbance was collected. The elution fraction, containing active Aurora-A kinase, was dialysed exhaustively against dialysis buffer (25 mM HEPES pH7.4 at 4°C , 45% glycerol (v/v), 100 mM KCl, 0.25% Nonidet P40 (v/v), 1 mM dithiothreitol).

Each new batch of Aurora-A enzyme was titrated in the assay by dilution with enzyme diluent (25mM Tris-HCl pH7.5, 12.5mM KCl, 0.6mM DTT). For a typical batch, stock enzyme is diluted 1 in 666 with enzyme diluent & 20µl of dilute enzyme is used for each assay well. Test compounds (at 10mM in dimethylsulphoxide (DMSO) were diluted with water & 10µl of diluted compound was transferred to wells in the assay plates. "Total" & "blank" control wells contained 2.5% DMSO instead of compound. Twenty microlitres of freshly diluted enzyme was added to all wells, apart from "blank" wells. Twenty microlitres of enzyme diluent was added to "blank" wells. Twenty microlitres of reaction mix (25mM Tris-HCl, 78.4mM KCl, 2.5mM NaF, 0.6mM dithiothreitol, 6.25mM $MnCl_2$, 6.25mM ATP, 7.5µM peptide substrate [biotin-LRRWSLGLRRWSLGLRRWSLGLRRWSLG]) containing 0.2µCi [γ^{33}P]ATP (Amersham Pharmacia, specific activity ≥2500Ci/mmol) was then added to all test wells to start the reaction. The plates were incubated at room temperature for 60 minutes. To stop the reaction 100µl 20% v/v orthophosphoric acid was added to all wells. The peptide substrate was captured on positively-charged nitrocellulose P30 filtermat (Whatman) using a 96-well plate harvester (TomTek) & then assayed for incorporation of ^{33}P with a Beta plate counter. "Blank" (no enzyme) and "total" (no compound) control values were used to determine the dilution range of test compound which gave 50% inhibition of enzyme activity.

In this test, the compounds of the invention give 50% inhibition of enzyme activity at concentrations of 0.3nM to 1000nM and in particular compound 5 in Table 1 gave 50% inhibition of enzyme activity at a concentration of 0.5nM.

(b) <u>In Vitro Aurora-B kinase inhibition test</u>

This assay determines the ability of a test compound to inhibit serine-threonine kinase activity. DNA encoding Aurora-B may be obtained by total gene synthesis or by cloning. This DNA may then be expressed in a suitable expression system to obtain polypeptide with serine-threonine kinase activity. In the case of Aurora-B, the coding sequence was isolated from cDNA by polymerase chain reaction (PCR) and cloned into the pFastBac system in a manner similar to that described above for Aurora-A (i.e. to direct expression of a 6-histidine tagged Aurora-B protein).

For the large scale expression of Aurora-B kinase activity, Sf21 insect cells were grown at 28°C in TC100 medium supplemented with 10% foetal calf serum (Viralex) and 0.2% F68 Pluronic (Sigma) on a Wheaton roller rig at 3 r.p.m. When the cell density reached $1.2x10^6$ cells ml^{-1} they were infected with plaque-pure Aurora-B recombinant virus at a

multiplicity of infection of 1 and harvested 48 hours later. All subsequent purification steps were performed at 4°C. Frozen insect cell pellets containing a total of 2.0 x 10^8 cells were thawed and diluted with lysis buffer (50 mM HEPES (N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulphonic acid]) pH7.5 at 4°C , 1 mM Na_3VO_4, 1 mM PMSF (phenylmethylsulphonyl fluoride), 1 mM dithiothreitol, 1 μg/ml aprotinin, 1 μg/ml pepstatin, 1 μg/ml leupeptin), using 1.0 ml per 2 x 10^7 cells. Lysis was achieved using a sonication homogeniser, following which the lysate was centrifuged at 41,000*g* for 35 minutes. Aspirated supernatant was pumped onto a 5 mm diameter chromatography column containing 1.0 ml CM sepharose Fast Flow (Amersham Pharmacia Biotech) which had been equilibrated in lysis buffer. A baseline level of UV absorbance for the eluent was reached after washing the column with 12 ml of lysis buffer followed by 7 ml of wash buffer (50 mM HEPES pH7.4 at 4°C , 1 mM dithiothreitol). Bound Aurora-B B protein was eluted from the column using a gradient of elution buffer (50 mM HEPES pH7.4 at 4°C , 0.6 M NaCl, 1 mM dithiothreitol, running from 0% elution buffer to 100% elution buffer over 15 minutes at a flowrate of 0.5 ml/min). Elution fractions (1.0 ml) corresponding to the peak in UV absorbance was collected. Elution fractions were dialysed exhaustively against dialysis buffer (25 mM HEPES pH7.4 at 4°C , 45% glycerol (v/v), 100 mM KCl, 0.05% (v/v) IGEPAL CA630 (Sigma Aldrich), 1 mM dithiothreitol). Dialysed fractions were assayed for Aurora-B kinase activity.

Each new batch of Aurora-B enzyme was titrated in the assay by dilution with enzyme diluent (25mM Tris-HCl pH7.5, 12.5mM KCl, 0.6mM DTT). For a typical batch, stock enzyme is diluted 1 in 40 with enzyme diluent & 20μl of dilute enzyme is used for each assay well. Test compounds (at 10mM in dimethylsulphoxide (DMSO) were diluted with water & 10μl of diluted compound was transferred to wells in the assay plates. "Total" & "blank" control wells contained 2.5% DMSO instead of compound. Twenty microlitres of freshly diluted enzyme was added to all wells, apart from "blank" wells. Twenty microlitres of enzyme diluent was added to "blank" wells. Twenty microlitres of reaction mix (25mM Tris-HCl, 78.4mM KCl, 2.5mM NaF, 0.6mM dithiothreitol, 6.25mM $MnCl_2$, 37.5mM ATP, 25μM peptide substrate [biotin-LRRWSLGLRRWSLGLRRWSLGLRRWSLG]) containing 0.2μCi [γ^{33}P]ATP (Amersham Pharmacia, specific activity ≥2500Ci/mmol) was then added to all test wells to start the reaction. The plates were incubated at room temperature for 60 minutes. To stop the reaction 100μl 20% v/v orthophosphoric acid was added to all wells. The peptide substrate was captured on positively-charged nitrocellulose P30 filtermat (Whatman) using a 96-well plate harvester (TomTek) & then assayed for incorporation of ^{33}P with a Beta plate

counter. "Blank" (no enzyme) and "total" (no compound) control values were used to determine the dilution range of test compound which gave 50% inhibition of enzyme activity.

In this test, the compounds of the invention give 50% inhibition of enzyme activity at concentrations of 0.3nM to 1000nM and in particular compound 5 in Table 1 gave 50% inhibition of enzyme activity at a concentration of 1.6nM.

(c) In Vitro cell proliferation assay

This and other assays can be used to determine the ability of a test compound to inhibit the growth of adherent mammalian cell lines, for example the human tumour cell line SW620 (ATCC CCL-227). This assay determines the ability of at test compound to inhibit the incorporation of the thymidine analogue, 5'-bromo-2'-deoxy-uridine (BrdU) into cellular DNA. SW620 or other adherent cells were typically seeded at $1x10^5$ cells per well in L-15 media (GIBCO) plus 5% foetal calf serum, 1% L-glutamine (100µl / well) in 96 well tissue culture treated 96 well plates (Costar) and allowed to adhere overnight. The following day the cells were dosed with compound (diluted from 10mM stock in DMSO using L-15 (with 5% FCS, 1% L-glutamine). Untreated control wells and wells containing a compound known to give 100% inhibition of BrdU incorporation were included on each plate. After 48 hours in the presence / absence of test compound the ability of the cells to incorporate BrdU over a 2 hour labelling period was determined using a Boehringer (Roche) Cell Proliferation BrdU ELISA kit (cat. No. 1 647 229) according to manufacturers directions. Briefly, 15µl of BrdU labelling reagent (diluted 1:100 in media – L-15, 5% FCS, 1% L-glutamine) was added to each well and the plate returned to a humidified (+5% CO_2) 37°C incubator for 2 hours. After 2 hours the labelling reagent was removed by decanting and tapping the plate on a paper towel. FixDenat solution (50µl per well) was added and the plates incubated at room temperature for 45mins with shaking. The FixDenat solution was removed by decanting and tapping the inverted plate on a paper towel. The plate was then washed once with phosphate buffered saline (PBS) and 100µl /well of Anti-BrdU-POD antibody solution (diluted 1:100 in antibody dilution buffer) added. The plate was then incubated at room temperature with shaking for 90min. Unbound Anti-BrdU-POD antibody was removed by decanting and washing the plate 4 times with PBS before being blotted dry. TMB substrate solution was added (100µl/well) and incubated for approximately 10 minutes at room temperature with shaking until a colour change was apparent. The optical density of the wells was then determined at 690nm wavelength using a Titertek Multiscan plate reader. The values from

compound treated, untreated and 100% inhibition controls were used to determine the dilution range of a test compound that gave 50% inhibition of BrdU incorporation. The compounds of the invention are active at 0.3nM to 10000nM in this test and in particular compound 5 in table 1 was active at 87nM.

(d) In Vitro cell cycle analysis assay

This assay determines the ability of a test compound to arrest cells in specific phases of the cell cycle. Many different mammalian cell lines could be used in this assay and SW620 cells are included here as an example. SW620 cells were seeded at 7 x 10^5 cells per T25 flask (Costar) in 5 ml L-15 (5% FCS, 1% L-glutamine). Flasks were then incubated overnight in a humidified 37^{0}C incubator with 5% CO_2. The following day, 5µl of L-15 (5% FCS, 1% L-glutamine) carrying the appropriate concentration of test compound solubilised in DMSO was added to the flask . A no compound control treatments was also included (0.5% DMSO). The cells were then incubated for a defined time (24 hours) with compound. After this time the media was aspirated from the cells and they were washed with 5ml of prewarmed (37^{0}C) sterile PBSA, then detached from the flask by brief incubation with trypsin and followed by resuspension in 5ml of 1% Bovine Serum Albumin (BSA, Sigma-Aldrich Co.) in sterile PBSA. The samples were then centrifuged at 2200rpm for 10 min. The supernatant was aspirated to leave 200µl of the PBS/BSA solution. The pellet was resuspended in this 200µl of solution by pipetting 10 times to create a single cell suspension. One ml of ice-cold 80% ethanol was slowly added to each cell suspension and the samples stored at -20°C overnight or until required for staining. Cells were pelleted by centrifugation, ethanol aspirated off and pellets resuspended in 200µl PBS containing 100µg/ml RNAse (Sigma Aldrich) & 10µg/ml Propidium Iodide (Sigma Aldrich). Cell suspensions were incubated at 37°C for 30min, a further 200µl PBS added and samples stored in the dark at 4°C overnight.

Each sample was then syringed 10 times using 21-guage needle. The samples were then transferred to LPS tubes and DNA content per cell analysed by Fluorescence activated cell sorting (FACS) using a FACScan flow cytometer (Becton Dickinson). Typically 30,000 events were counted and recorded using CellQuest v1.1 software (Verity Software). Cell cycle distribution of the population was calculated using Modfit software (Verity Software) and expressed as percentage of cells with 2N (G0/G1), 2N-4N (S phase) and with 4N (G2/M) DNA content.

The compounds of the invention are active in this test at 0.3nM to 10000nM.

The invention will now be illustrated in the following non limiting examples, in whic standard techniques known to the skilled chemist and techniques analogous to those describe in these Examples may be used where appropriate, and in which, unless otherwise stated:

(i) evaporations were carried out by rotary evaporation *in vacuo* and work up procedures wer carried out after removal of residual solids such as drying agents by filtration;

(ii) operations were carried out at ambient temperature, typically in the range 18-25°C and i air unless stated, or unless the skilled person would otherwise operate under an atmosphere c an inert gas such as argon;

(iii) column chromatography (by the flash procedure) and medium pressure liqui chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385);

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) the structures of the end products of the formula (I) were generally confirmed by nuclea (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magneti resonance chemical shift values were measured in deuterated dimethyl sulphoxide (DMSO d_6 (unless otherwise stated) on the delta scale (ppm downfield from tetramethylsilane) using on of the following four instruments

- Varian Gemini 2000 spectrometer operating at a field strength of 300 MHz
- Bruker DPX300 spectrometer operating at a field strength of 300MHz
- JEOL EX 400 spectrometer operating at a field strength of 400 MHz
- Bruker Avance 500 spectrometer operating at a field strength of 500MHz

Peak multiplicities are shown as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q quartet; qu, quintet; m, multiplet; br s, broad singlet.

(vi) robotic synthesis was carried out using a Zymate XP robot, with solution additions via a Zymate Master Laboratory Station and stirred via a Stem RS5000 Reacto-Station at 25°C;

(vii) work up and purification of reaction mixtures from robotic synthesis was carried out as follows: evaporations were carried out *in vacuo* using a Genevac HT 4; column chromatography was performed using either an Anachem Sympur MPLC system on silica using 27 mm diameter columns filled with Merck silica (60 μm, 25 g); the structures of the final products were confirmed by LCMS on a Waters 2890 / ZMD micromass system using the following and are quoted as retention time (RT) in minutes:

Column: waters symmetry C18 3.5 μm 4.6x50 mm

Solvent A: H_2O

Solvent B: CH_3CN

Solvent C : methanol + 5% HCOOH

Flow rate: 2.5 ml / min

Run time: 5 minutes with a 4.5 minute gradient from 0-100% C

Wavelength: 254 nm, bandwidth 10 nm

Mass detector: ZMD micromass

Injection volume 0.005 ml

(viii) Analytical LCMS for compounds which had not been prepared by robotic synthesis was performed on a Waters Alliance HT system using the following and are quoted as retention time (RT) in minutes:

Column: 2.0 mm x 5 cm Phenomenex Max-RP 80A

Solvent A: Water

Solvent B: Acetonitrile

Solvent C: Methanol / 1% formic acid or Water / 1% formic acid

Flow rate: 1.1 ml / min

Run time: 5 minutes with a 4.5 minute gradient from 0-95% B + constant 5% solvent C

Wavelength: 254 nm, bandwidth 10 nm

Injection volume 0.005 ml

Mass detector: Micromass ZMD

(ix) Preparative high performance liquid chromatography (HPLC) was performed on either

- Waters preparative LCMS instrument, with retention time (RT) measured in minutes:

Column: β-basic Hypercil (21x100 mm) 5μm

Solvent A: Water / 0.1% Ammonium carbonate

Solvent B: Acetonitrile

Flow rate: 25 ml / min

Run time: 10 minutes with a 7.5 minute gradient from 0-100% B

Wavelength: 254 nm, bandwidth 10 nm

Injection volume 1 - 1.5 ml

Mass detector : Micromass ZMD

- Gilson preparative HPLC instrument, with retention time (RT) measured in minutes:

Column: 21 mm x 15 cm Phenomenex Luna2 C18

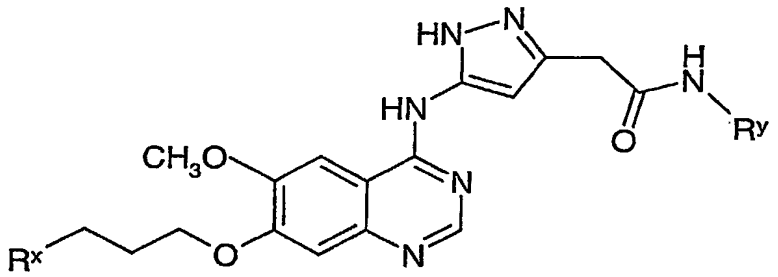
Solvent A: Water + 0.1% trifluoracetic acid,

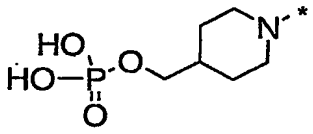
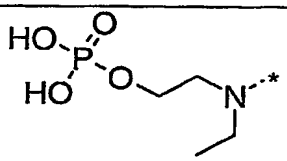
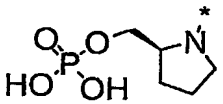
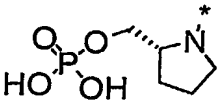
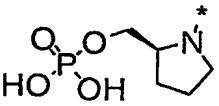
Solvent B:	Acetonitrile + 0.1% trifluoracetic acid
Flow rate:	21 ml / min
Run time:	20 minutes with various 10 minute gradients from 5-100% B
Wavelength:	254 nm, bandwidth 10 nm
Injection volume	0.1-4.0 ml

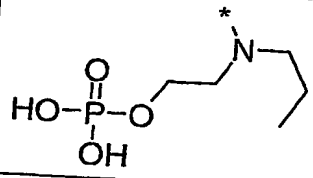
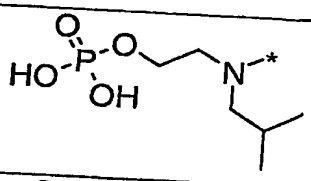
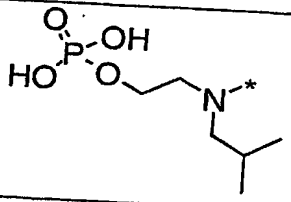
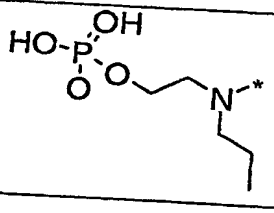
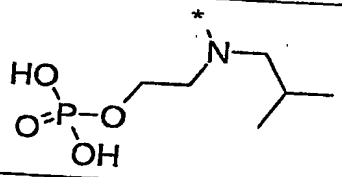
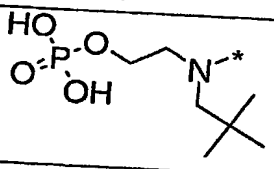
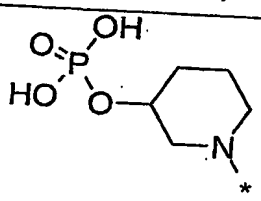
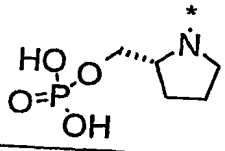
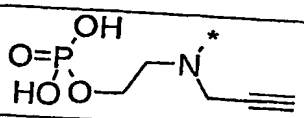
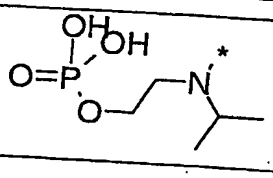
(x) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), HPLC, infra-red (IR), MS or NMR analysis.

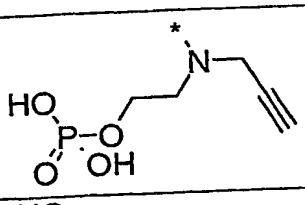
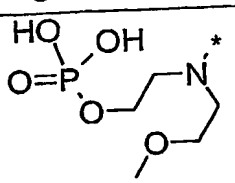
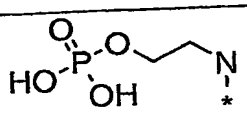
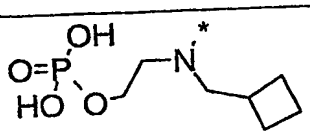
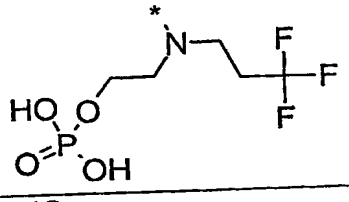
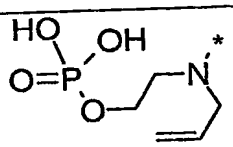
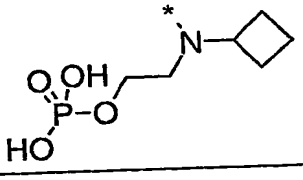
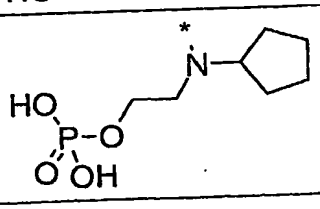
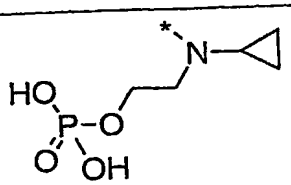
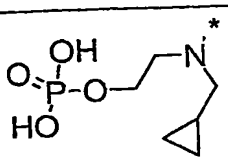
Particular examples of compounds of formula (I) are set out in Table 1:

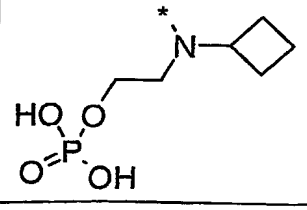
Table 1



Compound	R^x	R^y
1		3-fluorophenyl
2		3,5-difluorophenyl
3		3,5-difluorophenyl
4		3,5-difluorophenyl
5		3-fluorophenyl

6		2,3- difluorophenyl
7		2,3- difluorophenyl
8		3,5-difluorophenyl
9		3,5-difluorophenyl
10		3-fluorophenyl
11		3-fluorophenyl
12		3-fluorophenyl
13		2,3- difluorophenyl
14		3,5-difluorophenyl
15		2,3- difluorophenyl

16		2,3- difluorophenyl
17		2,3- difluorophenyl
18		3-fluorophenyl
19		2,3- difluorophenyl
20		3-fluorophenyl
21		2,3- difluorophenyl
22		2,3- difluorophenyl
23		2,3- difluorophenyl
24		3-fluorophenyl
25		2,3- difluorophenyl

26		3-fluorophenyl

Example 1 - Preparation of Compound 1 in Table 1 - {1-[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]piperidin-4-yl}methyl dihydrogen phosphate

Di(*tert*-butyl) {1-[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]piperidin-4-yl}methyl phosphate (400 mg, 0.53 mmol) was suspended in dioxane (20 ml) and treated with a solution of hydrochloric acid (4.0 N) in dioxane (795 µl, 3.18 mmol) at ambient temperature for 15 hours. The solid was recovered by filtration, washed with dioxane, dried *in vacuo* at 50 °C to yield compound 1 in table 1 (360 mg, 94 % yield) :

^{1}H-NMR (DMSO d_6, AcOD) : 8.88 (s, 1H), 8.27 (s, 1H), 7.61 (m, 1H), 7.35 (m, 3H), 6.84 (m, 1H), 6.81 (s, 1H), 4.28 (m, 2H), 3.98 (s, 3H), 3.83 (s, 2H), 3.75 (t, 2H), 3.58 (d, 2H), 3.26 (m, 2H), 3.26 (m, 2H), 2.32 (m, 2H), 1.85 (m, 3H), 1.54 (m, 2H) :

MS (+ve ESI) : 644.5 $(M+H)^+$.

Di(*tert*-butyl) {1-[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]piperidin-4-yl}methyl phosphate, used as the starting material, was obtained as follows:

a) A mixture of 4-benzyloxy-3-methoxybenzaldehyde (157 g, 649 mmol), sodium acetate (106 g, 1.29 mol), hydroxylamine hydrochloride (90 g, 1.29 mol) and acetic acid (500 ml) was refluxed for 21 hours. The solvent was evaporated and ice / water (1000 ml) added to the residue forming a sticky solid. The mixture was neutralised with aqueous sodium hydroxide solution then extracted with dichloromethane (2 x 500 ml). The organic solution was washed with 1.0 N sodium hydroxide (100 ml), brine (100 ml) and then dried over magnesium sulphate. Solvent evaporation, trituration of the residue with hexane : ethyl acetate (3:1) and collection of the solid by vacuum filtration yielded 4-benzyloxy-3-methoxybenzonitrile (123 g, 80 % yield) as a brown solid :

^{1}H-NMR (DMSO d_6) : 7.38 (m, 7H), 7.19 (m, 1H), 5.18 (s, 2H), 3.80 (s, 3H) :

MS (-ve ESI) : 238 $(M-H)^-$.

b) Acetic acid (17 ml) was added slowly to nitric acid (40 ml, 440 mmol) at 5 °C. Powdered 4-benzyloxy-3-methoxybenzonitrile (10 g, 42 mmol) was added and the mixture warmed to 23 °C over 10 minutes. An exotherm occurred and the temperature was controlled at < 30 °C using an ice bath. The mixture was stirred at 23 °C for 20 hours then poured into ice / water (1000 ml). After stirring for two hours the yellow solid was collected by suction filtration, washed with water and dried to yield 4-benzyloxy-3-methoxy-6-nitrobenzonitrile (10.1 g, 85 % yield) as a yellow solid :

^{1}H-NMR (DMSO d_6) : 7.95 (s, 1H), 7.70 (s, 1H), 7.40 (m, 5H), 5.30 (s, 2H), 3.95 (s, 3H):

MS (-ve ESI) : 283 $(M-H)^-$.

c) A mixture of 4-benzyloxy-3-methoxy-6-nitrobenzonitrile (46 g, 162 mmol), sodium bicarbonate (95 g, 1.13 mol), water (750 ml), dichloromethane (550 ml) and tetrabutylammonium chloride (30 g, 108 mmol) was rapidly stirred at 20 °C and treated with sodium dithionite (66 g, 379 mmol) portionwise over 2 hours. The mixture was stirred for a further hour then the phases separated. The aqueous phase was extracted with dichloromethane (2 x 200 ml) and the combined organic solution washed with water (300 ml) and dried over magnesium sulphate. The solution was concentrated to 250 ml and 4.0 M hydrochloric acid in 1,4-dioxane (150 ml, 0.6 mol) added, then diluted with diethyl ether (1000 ml) and cooled on ice. The resulting solid was collected by vacuum filtration and washed with diethyl ether. The solid was stirred in methanol (1000 ml) and sodium bicarbonate solution (800 ml) added to pH 8 and stirred for 1 hour. The solid was collected by vacuum filtration, washed with water then methanol and dried *in vacuo* to yield 2-amino-4-(benzyloxy)-5-methoxybenzonitrile (34 g, 82 % yield) as light brown solid :

^{1}H-NMR (DMSO d_6) : 7.40 (m, 5H), 6.90 (s, 1H), 6.50 (s, 1H), 5.60 (br s, 2H), 5.02 (s, 2H), 3.65 (s, 3H) :

MS (+ve ESI) : 254 $(M+H)^+$.

d) 2-amino-4-(benzyloxy)-5-methoxybenzonitrile (100 g, 394 mmol) in toluene (1400 ml) was treated with dimethylformamide dimethylacetal (100 ml, 940 mmol) at reflux with slow distillation of solvent to maintain the internal temperature at 105 °C. After 3 hours the solution was cooled and filtered to remove a small amount of solid. The filtrate was evaporated *in vacuo* and the residue triturated with diethyl ether and the solid collected by vacuum filtration and dried *in vacuo* to yield *N'*-(5-(benzyloxy)-2-cyano-4-methoxyphenyl)-*N,N*-dimethylimidoformamide (110 g, 90 % yield) as a brown solid :

^{1}H-NMR (DMSO d_6) : 7.90 (s, 1H), 7.40 (m, 5H), 7.10 (s, 1H), 6.88 (s, 1H), 5.15 (s, 2H), 3.70 (s, 3H), 3.02 (s, 3H), 2.95 (s, 3H) :

MS (+ve ESI) : 310 $(M+H)^+$

MS (-ve ESI) : 308 $(M-H)^-$.

e) *N'*-(5-(benzyloxy)-2-cyano-4-methoxyphenyl)-*N,N*-dimethylimidoformamide (110 g, 356 mmol) and trifluoroacetic acid (600 ml) were refluxed together for 15 min. Evaporation and co-evaporation with toluene, trituration with diethyl ether and collection of the solid by vacuum filtration and drying *in vacuo* yielded *N'*-(2-cyano-5-hydroxy-4-methoxyphenyl)-*N,N*-dimethylimidoformamide (112 g, 95 % yield) as a light brown trifluoroacetate salt :

^{1}H-NMR (DMSO d_6) : 8.39 (s, 1H), 7.38 (s, 1H), 6.90 (s, 1H), 3.80 (s, 3H), 3.25 (s, 3H), 3.17 (s, 3H) :

MS (+ve ESI) : 220 $(M+H)^+$

MS (-ve ESI) : 218 $(M-H)^-$.

f) A mixture of *N'*-(2-cyano-5-hydroxy-4-methoxyphenyl)-*N,N*-dimethylimidoformamide (21.9 g, 66 mmol), cesium carbonate (998 g, 300 mmol) and 1-bromo-3-chloropropane (11 ml, 110 mmol) in acetonitrile (300 ml) was refluxed for 1 hour. The reaction mixture was cooled and the solvent evaporated *in vacuo*. The residue in water (200 ml) was extracted with dichloromethane (2 x 150 ml). The organic solution was washed with brine (50 ml) and dried over magnesium sulphate. Solvent was evaporated *in vacuo* and the residue triturated with diethyl ether. The solid was collected by vacuum filtration and dried *in vacuo* to yield *N'*-(5-(3-chloropropoxy)-2-cyano-4-methoxyphenyl)-*N,N*-dimethylimidoformamide (17.7 g, 91 % yield) as a white solid :

^{1}H-NMR (DMSO d_6) : 8.89 (s, 1H), 7.07 (s, 1H), 6.75 (s, 1H), 4.15 (t, 2H), 3.77 (t, 2H), 3.70 (s, 3H), 3.05 (s, 3H), 2.95 (s, 3H), 2.18 (m, 2H) :

MS (+ve ESI) : 296.4 $(M+H)^+$.

g) N'-(5-chloropropoxy)-2-cyano-4-methoxyphenyl)-*N,N*-dimethylimidoformamide (230 mg, 0.78 mmol) in acetic acid (0.7 ml) was reacted with methyl (5-amino-1H-pyrazol-3-yl)acetate (CAS 174891-10-2; WO 95/33724) (110 mg, 0.74 mmol) at reflux for 1 hour. The mixture was cooled, the acetic acid evaporated, and the residue purified by chromatography on silica gel, eluting with dichloromethane / 1 % methanolic ammonia (90:10), to give methyl (5-((7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl)amino)-1H-pyrazol-3-yl)acetate (219 mg, 69 % yield) as a cream solid :

^{1}H-NMR (DMSO d_6, TFA): 8.93 (s, 1H), 8.28 (s, 1H), 7.32 (s, 1H), 6.80 (s, 1H), 4.02 (m, 2H), 4.00 (s, 3H), 3.75-3.85 (m, s, 4H), 3.65 (s, 3H), 2.30 (m, 2H), 1.90 (s, 3H) :
MS (+ve ESI) : 406.5 $(M+H)^+$.

h) Methyl (5-((7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl)amino)-1H-pyrazol-3-yl)acetate (100 mg, 0.247 mmol) in tetrahydrofuran (1.2 ml) / water (0.6 ml), was reacted with lithium hydroxide (21 mg, 0.493 mmol) at ambient temperature over night. The mixtur was acidified with 6.0 N hydrochloric acid to pH 4 and the solid was recovered by filtration, washed with water and dried to give (5-((7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl)amino)-1H-pyrazol-3-yl)acetic acid (72 mg, 75 % yield) as a beige solid :
^{1}H-NMR (DMSO d_6, TFA) : 8.95 (s, 1H), 8.28 (s, 1H), 7.32 (s, 1H), 6.80 (s, 1H), 4.33 (m, 2H), 4.00 (s, 3H), 3.83 (m, 2H), 3.74 (s, 2H), 2.40-2.50 (m, 2H) :
MS (+ve ESI) : 392.5, 394.5 $(M+H)^+$.

i) (5-((7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl)amino)-1H-pyrazol-3-yl) acetic acid (7.83 g, 20 mmol) in dimethylformamide (78 ml) was reacted with 3-fluoroaniline (2.44 g, 22 mmol) in the presence of 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (4.2 g, 22 mmol), 2-hydroxypyridin-1-oxide (2.22 g, 20 mmol) and diisopropylethylamine (2.8 g, 22 mmol) at 50 °C for 1.7 hours. The solvent was removed by evaporation under vacuum, the residue was triturated with water (twice), and purified by silic gel chromatography, eluting with dichloromethane : methanol (95:3 to 85:15) to give 2-(5-((7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl)amino)-1H-pyrazol-3-yl)-N-(3-fluorophenyl) acetamide (4.5 g, 46 % yield) as a beige solid :
^{1}H-NMR (DMSO d_6) : 8.47 (s, 1H), 8.02 (s, 1H), 7.60-7.68 (m, 1H), 7.30-7.41 (m, 2H), 7.20 (s, 1H), 6.88 (m, 1H), 6.84 (s, 1H), 4.27 (m, 2H), 3.96 (s, 3H), 3.84 (m, 2H), 3.78 (s, 2H), 2.26 (m, 2H) :
MS (+ve ESI) : 485.6 $(M+H)^+$.

j) Piperidin-4-ylmethanol (115 mg, 1 mmol) was added to a solution of 2-(5-((7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl)amino)-1H-pyrazol-3-yl)-N-(3-fluorophenyl) acetamide (121 mg, 0.25 mmol) in dimethylacetamide (1 ml) and the reaction was heated at 90 °C for 9 hours. The reaction was cooled to ambient temperature and the volatiles removed in vacuo. Purification by reverse phase hplc yielded *N*-(3-fluorophenyl)-2-{3-[(7-{3-[4-(hydroxymethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}acetamide (80 mg, 57 % yield) as an off-white solid :

^{1}H-NMR (DMSO d_6, TFA) : 8.96 (s, 1H), 8.30 (s, 1H), 7.63 (m, 1H), 7.36 (m, 3H), 6.90 (m, 1H), 6.84 (s, 1H), 4.30 (t, 2H), 4.01 (s, 3H), 3.85 (s, 2H), 3.62 (d, 2H), 3.32 (d, 2H), 3.27 (m, 2H), 2.98 (t, 2H), 2.29 (m, 2H), 1.90 (d, 2H), 1.67 (m, 1H), 1.42 (m, 2H) :

MS (+ve ESI) : 564.6 $(M+H)^+$.

k) *N*-(3-fluorophenyl)-2-{3-[(7-{3-[4-(hydroxymethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}acetamide (450 mg, 1 mmol) was dissolved in dimethylformamide (2 ml), tetrazole (224 mg, 4 mmol) and di-*tert*-butyl-diethyl-phosphoramidite (479 µl, 2 mmol) were added to the mixture at ambient temperature, and stirring was continued for 3 hours under argon. The reaction mixture was then cooled to –60 °C and a solution of monoperoxyphthalic acid magnesium salt (297 mg, 0.6 mmol) in dimethylformamide (1.5 ml) was slowly added to the reaction mixture. This mixture was then stirred for 1.5 hours at –60 °C, sodium metabisulphite (1.5 g, 10 mmol) in solution in water (2 ml) was then added and the reaction mixture was slowly allowed to warm to ambient temperature, evaporated, and the residue was purified by silica gel chromatography, eluting with dichloromethane : 3.0 N methanolic ammonia (100:0 to 92:8), to give di(*tert*-butyl) {1-[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]piperidin-4-yl}methyl phosphate (420 mg, 70 % yield) as a cream solid :

^{1}H-NMR (DMSO d_6) : 8.46 (s, 1H), 7.99 (s, 1H), 7.63 (d, 1H), 7.36 (m, 2H), 7.35 (s, 1H), 7.15 (s, 1H), 6.90 (m, 1H), 6.88 (s, 1H), 4.17 (t, 2H), 3.95 (s, 3H), 3.77 (s, 2H), 3.72 (t, 2H), 2.91 (d, 2H), 2.46 (t, 2H), 1.96 (m, 4H), 1.65 (m, 2H), 1.58 (m, 1H), 1.41 (s, 18H), 1.25 (m, 2H) :

MS (+ve ESI) : 756.6 $(M+H)^+$.

Example 2 - Preparation of Compound 2 in Table 1 - 2-[[3-({4-[(5-{2-[(3,5-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](ethyl)amino]ethyl dihydrogen phosphate

An analogous reaction to that described in example 1, but starting with di(*tert*-butyl) 2-[[3-({4-[(5-{2-[(3,5-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](ethyl)amino]ethyl phosphate (320 mg, 0.428 mmol) yielded compound 2 in table 1 (260 mg, 86 % yield) as an off-white solid :

^{1}H-NMR (DMSO d_6, CD_3COOD) : 8.92 (s, 1H), 8.31 (s, 1H), 7.41 (m, 3H), 6.88 (t, 1H), 6.84 (s, 1H), 4.32 (m, 4H), 3.97 (s, 3H), 3.89 (s, 2H), 3.42 (m, 6H), 2.32 (m, 2H), 1.31 (t, 3H) :

MS (+ve ESI) : 636.4 $(M+H)^+$.

Di(*tert*-butyl) 2-[[3-({4-[(5-{2-[(3,5-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](ethyl)amino]ethyl phosphate, used as the starting material, was obtained as follows:

a) A suspension of 3-{[7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-5-yl)acetic acid (3.91 g, 10 mmol) in dimethylformamide (20 ml) was reacted with 3,5-difluoroaniline (1.42 g , 11 mmol) in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodimide hydrochloride (2.01 g, 10.5 mmol) and 2-hydroxypyridine-1-oxide (1.11 g, 10 mmol) at 60 °C for 1.75 hours. The solvent was evaporated *in vacuo* and the residue was triturated twice with water. The resulting wet paste was dissolved in a mixture of dichloromethane : water (80:20), adsorbed onto silica gel and purified by chromatography on silica gel, eluting with dichloromethane : methanol (95:5 to 85:15) to give 2-(5-((7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl)amino)-1H-pyrazol-3-yl)-N-(3,5-difluorophenyl) acetamide (2.45 g, 49 % yield) as a beige solid :

^{1}H-NMR (DMSO d_6) : 8.47 (s, 1H), 8.02 (s, 1H), 7.36 (m, 2H), 7.20 (s, 1H), 6.94 (t, 1H), 6.8 (s, 1H), 4.27 (m, 2H), 3.96 (s, 3H), 3.83 (m, 2H), 3.79 (s, 2H), 2.27 (m, 2H) :

MS (+ve ESI) : 503.5, 505.5 $(M+H)^+$.

b) An analogous reaction to that described in example 1j, but starting with 2-(ethylamino)ethanol (89 mg, 1 mmol) and 2-(5-((7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl)amino)-1H-pyrazol-3-yl)-N-(3,5-difluorophenyl) acetamide (130 mg, 0.26 mmol) yielde *N*-(3,5-difluorophenyl)-2-{3-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}acetamide (124 mg, 86 % yield) as an off-white solid:

^{1}H-NMR (DMSO d_6, TFA) : 8.96 (s, 1H), 8.30 (s, 1H), 7.35 (m, 2H), 7.33 (s, 1H), 6.90 (m, 1H), 6.84 (s, 1H), 4.30 (m, 2H), 4.01 (s, 3H), 3.86 (s, 2H), 3.78 (t, 2H), 3.30 (m, 6H), 2.29 (m, 2H), 1.27 (t, 3H) :

MS (+ve ESI) : 556.5 $(M+H)^+$.

c) An analogous reaction to that described in example 1k, but starting with *N*-(3,5-difluorophenyl)-2-{3-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}acetamide (400 mg, 0.72 mmol) yielded di(*tert*-butyl) 2-[[3-({4-[(5-{2-[(3,5-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](ethyl)amino]ethyl phosphate (320 mg, 60 % yield) as a off-white solid:

^{1}H-NMR (DMSO d_6) : 8.36 (s, 1H), 7.88 (s, 1H), 7.26 (m, 2H), 7.04 (s, 1H), 6.83 (t, 2H), 6.73 (s, 1H), 4.07 (m, 2H), 3.85 (s, 3H), 3.77 (q, 2H), 2.68 (s, 2H), 2.55 (m, 4H), 2.43 (m, 2H), 1.81 (m, 2H), 0.88 (t, 3H) :

MS (+ve ESI) : 748.5 $(M+H)^+$.

Example 3 - Preparation of Compound 3 in Table 1 - {(2*S*)-1-[3-({4-[(5-{2-[(3,5-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate

An analogous reaction to that described in example 1, but starting with di(*tert*-butyl) {(2*S*)-1-[3-({4-[(5-{2-[(3,5-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate (130 mg, 0.171 mmol) yielded compound 3 in table 1 (91 mg, 74 % yield) :

^{1}H-NMR (DMSO d_6, CD_3COOD) : 8.91 (s, 1H), 8.29 (s, 1H), 7.40 (m, 3H), 6.89 (t, 1H), 6.82 (s, 1H), 4.31 (m, 2H), 4.20 (m, 2H), 4.00 (s, 3H), 3.88 (s, 2H), 3.80 (m, 1H), 3.70 (m, 1H), 3.60 (m, 1H), 3.28 (m, 1H), 3.23 (m, 1H), 2.30 (m, 2H), 2.20 (m, 1H), 2.03 (m, 1H), 1.95 (m, 1H), 1.82 (m, 1H) :

MS (+ve ESI) : 648.3 $(M+H)^+$.

di(*tert*-butyl) {(2*S*)-1-[3-({4-[(5-{2-[(3,5-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate, used as the starting material, was obtained as follows:

a) An analogous reaction to that described in example 2b, but starting with L-prolinol (101 mg, 1 mmol) yielded *N*-(3,5-difluorophenyl)-2-{3-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}acetamide (85 mg, 57 % yield) as an off-white solid :

^{1}H-NMR (DMSO d_6, TFA) : 8.96 (s, 1H), 8.30 (s, 1H), 7.30-7.40 (m, 3H), 6.85-6.95 (m, 1H), 6.84 (s, 1H), 4.30 (m, 2H), 4.01 (s, 3H), 3.86 (s, 2H), 3.72-3.82 (m, 1H), 3.50-3.70 (m, 4H), 3.15-3.30 (m, 2H), 2.25-2.40 (m, 2H), 1.95-2.20 (m, 2H), 1.85-1.95 (m, 1H), 1.70-1.85 (m, 1H) :

MS (+ve ESI) : 568.6 $(M+H)^+$.

b) *N*-(3,5-difluorophenyl)-2-{3-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}acetamide (650 mg, 1.14 mmol) was dissolved in dimethylacetamide (4 ml). Tetrazole (160 mg, 2.3 mmol) and di-*tert*-butyl-diethylphosphoramidite (637 µl, 2.3 mmol) were added to the mixture and stirring was

continued at ambient temperature under argon for 3 hours. The reaction mixture was then diluted with dichloromethane (50 ml) and washed with a saturated solution of sodium bicarbonate. The organic phase was recovered, dried over magnesium sulphate, filtered and concentrated. The crude product was dissolved in tetrahydrofuran (18 ml) at 0 °C and hydrogen peroxide (30 %, 335 µl) was added to the solution, which was stirred for 15 hours at ambient temperature. The mixture was then cooled to 0 °C and sodium metabisulphite (1.08 g) in water (5 ml) was added at 0 °C, and the reaction was allowed to warm to ambient temperature. The mixture was diluted with ethyl acetate (50 ml), washed with a saturated solution of sodium bicarbonate. The organic phase was recovered, dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel, eluting with dichloromethane : methanol : 3.0 N methanolic ammonia (95:5:0 to 95:0:5), to give di(*tert*-butyl) {(2*S*)-1-[3-({4-[(5-{2-[(3,5-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate (133 mg, 15 % yield) as an off-white solid :

^{1}H-NMR (DMSO d_6) : 8.44 (s, 1H), 7.96 (s, 1H), 7.35 (m, 2H), 7.13 (s, 1H), 6.92 (m, 1H), 6.82 (s, 1H), 4.18 (m, 2H), 3.93 (s, 3H), 3.75 (m, 3H), 3.56 (m, 1H), 3.08 (m, 1H), 2.92 (m, 1H), 2.67 (m, 1H), 2.46 (m, 1H), 2.20 (q, 1H), 1.95 (m, 2H), 1.83 (m, 1H), 1.68 (m, 2H), 1.59 (m, 1H), 1.38 (s, 18H) :

MS (+ve ESI) : 760.5 $(M+H)^+$.

Example 4 - Preparation of Compound 4 in Table 1 - {(2*R*)-1-[3-({4-[(5-{2-[(3,5-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate

An analogous reaction to that described in example 1, but starting with di(*tert*-butyl) {(2*R*)-1-[3-({4-[(5-{2-[(3,5-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate (350 mg, 0.46 mmol) yielded compound 4 in table 1 (305 mg, 92 % yield) as an off-white solid :

^{1}H-NMR (DMSO d_6) : 8.90 (s, 1H), 8.29 (s, 1H), 7.40 (m, 3H), 6.87 (t, 1H), 6.81 (s, 1H), 4.31 (m, 2H), 4.20 (m, 2H), 4.00 (s, 3H), 3.88 (s, 2H), 3.80 (m, 1H), 3.70 (m, 1H), 3.60 (m, 1H), 3.28 (m, 1H), 3.23 (m, 1H), 2.32 (m, 2H), 2.20 (m, 1H), 2.04 (m, 1H), 1.95 (m, 1H), 1.84 (m, 1H) :

MS (+ve ESI) : 648.4 $(M+H)^+$.

di(*tert*-butyl) {(2*R*)-1-[3-({4-[(5-{2-[(3,5-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate, used as the starting material, was obtained as follows:

a) An analogous reaction to that described in example 2b, but starting with D-prolinol (101 mg, 1 mmol) yielded *N*-(3,5-difluorophenyl)-2-{3-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}acetamide (85 mg, 57 % yield) as an off-white solid :

^{1}H-NMR (DMSO d_6, TFA) : 8.96 (s, 1H), 8.30 (s, 1H), 7.35 (m, 2H), 7.33 (s, 1H), 6.91 (m, 1H), 6.84 (s, 1H), 4.31 (m, 2H), 4.01 (s, 3H), 3.86 (s, 2H), 3.78 (m, 1H), 3.63 (m, 4H), 3.22 (m, 2H), 2.30 (m, 2H), 2.13 (m, 1H), 2.03 (m, 1H), 1.80 (m, 1H), 1 .78 (m, 1H) :

MS (+ve ESI) : 568.5 $(M+H)^+$.

b) An analogous reaction to that described in example 3b, but starting with *N*-(3,5-difluorophenyl)-2-{3-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}acetamide (600 mg, 1.06 mmol) yielded di(*tert*-butyl) {(2*R*)-1-[3-({4-[(5-{2-[(3,5-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate (361 mg, 45 % yield) as an off-white solid :

^{1}H-NMR (DMSO d_6) : 8.45 (s, 1H), 7.96 (s, 1H), 7.35 (m, 2H), 7.13 (s, 1H), 6.93 (m, 1H), 6.82 (s, 1H), 4.18 (m, 2H), 3.95 (s, 3H), 3.75 (m, 3H), 3.58 (m, 1H), 3.08 (m, 1H), 2.93 (m, 1H), 2.67 (m, 1H), 2.46 (m, 1H), 2.22 (q, 1H), 1.96 (m, 2H), 1.86 (m, 1H), 1.69 (m, 2H), 1.61 (m, 1H), 1.38 (s, 18H) :

MS (+ve ESI) : 760.5 $(M+H)^+$.

Example 5 - Preparation of Compound 5 in Table 1 - {(2*S*)-1-[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate

An analogous reaction to that described in example 1, but starting with di(*tert*-butyl) {(2*S*)-1-[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate (282 mg, 0.38 mmol) yielded compound 5 in table 1(265 mg, 97 % yield) as an off-white solid :

^{1}H-NMR (DMSO d_6) : 8.90 (s, 1H), 8.30 (s, 1H), 7.66 (d, 1H), 7.46 (s, 1H), 7.40 (m, 2H), 6.90 (m, 1H), 6.81 (s, 1H), 4.31 (m, 2H), 4.20 (m, 2H), 4.00 (s, 3H), 3.88 (s, 2H), 3.80

(m, 1H), 3.70 (m, 1H), 3.60 (m, 1H), 3.28 (m, 1H), 3.22 (m, 1H), 2.32 (m, 2H), 2.20 (m, 1H), 2.04 (m, 1H), 1.95 (m, 1H), 1.84 (m, 1H) :

MS (+ve ESI) : 630.6 $(M+H)^+$.

di(*tert*-butyl) {(2*S*)-1-[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate, used as the starting material, was obtained as follows:

a) An analogous reaction to that described in example 1j, but starting with L-prolinol (121 mg, 0.25 mmol) yielded *N*-(3-fluorophenyl)-2-{3-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}acetamide (86 mg, 62 % yield) as an off-white solid :

^{1}H-NMR (DMSO d_6, TFA) : 8.95 (s, 1H), 8.29 (s, 1H), 7.60-7.70 (m, 1H), 7.28-7.40 (m, 3H), 6.85-6.92 (m, 1H), 6.82 (s, 1H), 4.31 (m, 2H), 4.00 (s, 3H), 3.84 (s, 2H), 3.70-3.80 (m, 1H), 3.50-3.70 (m, 4H), 3.10-3.30 (m, 2H), 2.20-2.40 (m, 2H), 2.05-2.20 (m, 1H), 1.95-2.10 (m, 1H), 1.85-1.95 (m, 1H), 1.70-7.85 (m, 1H) :

MS (+ve ESI) : 549.6 $(M+H)^+$.

b) An analogous reaction to that described in example 1k, but starting with *N*-(3-fluorophenyl)-2-{3-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}acetamide (275 mg, 0.5 mmol) yielded di(*tert*-butyl) {(2*S*)-1-[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate (255 mg, 69 % yield) as an off-white solid :

^{1}H-NMR (DMSO d_6) : 8.46 (s, 1H), 7.98 (s, 1H), 7.64 (d, 1H), 7.36 (m, 2H), 7.15 (s, 1H), 6.89 (m, 1H), 6.81 (s, 1H), 4.18 (m, 2H), 3.93 (s, 3H), 3.75 (m, 3H), 3.58 (m, 1H), 3.11 (m, 1H), 2.97 (m, 1H), 2.67 (m, 1H), 2.46 (m, 1H), 2.22 (m, 1H), 1.98 (m, 2H), 1.82 (m, 1H), 1.71 (m, 2H), 1.62 (m, 1H), 1.38 (s, 18H) :

MS (+ve ESI) : 742.7 $(M+H)^+$.

Example 6 - Preparation of compound 6 in table 1 - 2-[[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](propyl)amino]ethyl dihydrogen phosphate

An analogous reaction to that described in example 1, but starting with di-*tert*-butyl 2-[[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-

methoxyquinazolin-7-yl}oxy)propyl](propyl)amino]ethyl phosphate (316 mg, 0.41 mmol) yielded compound 6 in table 1 (300 mg, 100 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.96 (s, 1H), 8.31 (s, 1H), 7.75 (m, 1H), 7.36 (s, 1H), 7.20 (m, 2H), 6.84 (s, 1H), 4.31 (t, 2H), 4.24 (m, 2H), 4.01 (s, 3H), 3.94 (s, 2H), 3.50 (m, 2H), 3.38 (m, 2H), 3.19 (m, 2H), 2.32 (m, 2H), 1.74 (m, 2H), 0.95 (t, 3H) :

MS (+ve ESI) : 650.3 $(M+H)^+$.

di-*tert*-butyl 2-[[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](propyl)amino]ethyl phosphate used as starting material was obtained as follows :

a) 5-{[7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-3-yl)acetic acid (3.91 g, 10 mmol) was suspended in pyridine (20 ml) in the presence of 2,3-difluoroaniline (1.55 g, 12 mmol) under argon at 0 °C. Phosphorus oxychloride (1.53 g, 10 mmol) in ethyl acetate (2 ml) was slowly added at 0 °C and the resulting mixture was allowed to warm to ambient temperature over 1.5 hours. The reaction mixture was diluted with ethyl acetate (150 ml) and diethyl ether (50 ml) resulting in the precipitation of a red solid. The solid was recovered by suction filtration, dried and re-suspended in water (100 ml). The mixture was cooled to 0 °C and the pH adjusted to 7 by addition of 1.5 N aqueous ammonium hydroxide solution. After 15 minutes stirring, the solid was recovered, dried, and purified by chromatography on silica gel, eluting with dichloromethane : methanol (95/5) and increased polarity to dichloromethane : methanolic ammonia (95:2) to yield 2-(3-{[7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-5-yl)-*N*-(2,3-difluorophenyl)acetamide as a pink solid (2.55 g, 50 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.94 (s, 1H), 8.28 (s, 1H), 7.73 (m, 1H), 7.33 (s, 1H), 7.15-7.22 (m, 1H), 6.84 (s, 1H), 4.30 (m, 2H), 4.00 (s, 3H), 3.94 (s, 2H), 3.84 (m, 2H), 2.30 (m, 2H) :

MS (+ve ESI) : 503.9 $(M+H)^+$.

b) 2-(propylamino)ethanol (700mg, 68mmol) and potassium iodide (564 mg, 34 mmol) were added to a solution of 2-(3-{[7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-5-yl)-*N*-(2,3-difluorophenyl)acetamide (855 mg, 17 mmol) in dimethylacetamide (8 ml) and the reaction heated at 85 °C for 5 hours. The solvent was evaporated *in vacuo*, the residue triturated with diethyl ether and the solid was collected by suction filtration. Purification by chromatography on silica gel, eluting with, dichloromethane / methanol (90:10) to dichloromethane / methanol / ammonia (7.0 N) to give *N*-(2,3-difluorophenyl)-2-

{3-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}acetamide (650mg, 67 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.96 (s, 1H), 8.30 (s, 1H), 7.75 (m, 1H), 7.33 (s, 1H), 7.18-7.22 (m, 2H), 6.84 (s, 1H), 4.30 (m, 2H), 4.00 (s, 3H), 3.94 (s, 2H), 3.78 (m, 2H), 3.30-3.45 (m, 2H), 3.28 (m, 2H), 3.15-3.20 (m, 2H), 2.28 (m, 2H), 1.73 (m, 2H), 0.95 (t, 3H) :

MS (+ve ESI) : 570.3 $(M+H)^+$.

c) Di-*tert*-butyl-diethylphosphoramidite (417 μm, 1.5 mmol) was slowly added to a solution of *N*-(2,3-difluorophenyl)-2-{3-[(7-{3-[(2-hydroxyethyl)(propyl) amino]propoxy}-6 methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}acetamide (569 mg, 1 mmol) in dimethylformamide (2.5 ml) in the presence of tetrazole (210 mg, 3 mmol) at ambient temperature under argon. The mixture was stirred at ambient temperature for 1.5 hours, cooled to –10 °C and hydrogen peroxide (134 μm of a 9.0 N solution, 1.2 mmol) was slowly added. The resulting mixture was stirred at ambient temperature for 2 hours. Sodium metabisulphite (570 mg, 3 mmol) in water (2 ml) was then added at 0 °C and the mixture was stirred at ambient temperature for 0.5 hour. The mixture was concentrated, dichloromethane / methanol (8:2) was added before the solid was filtered and washed with dichloromethane / methanol. Concentration of the filtrate *in vacuo* followed by chromatography on silica gel, eluting with dichloromethane / methanol (90:10) to dichloromethane / methanol / ammonia (7.0 N) (90:10:1), yielded di-*tert*-butyl 2-[[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](propyl)amino]ethyl phosphate as an off-white solid (319 mg, 42 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.95 (s, 1H), 8.29 (s, 1H), 7.72 (m, 1H), 7.33 (s, 1H), 7.18 (m, 2H), 6.84 (s, 1H), 4.20-4.35 (m, 4H), 4.00 (s, 3H), 3.94 (s, 2H), 3.53 (m, 2H), 3.39 (m, 2H), 3.20 (m, 2H), 2.30 (m, 2H), 1.73 (m, 2H), 1.44 (s, 18H), 0.95 (t, 3H) :

MS (+ve ESI) : 762.5 $(M+H)^+$.

Example 7 - Preparation of compound 7 in table 1 - 2-[[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](isobutyl)amino]ethyl dihydrogen phosphate

An analogous reaction to that described in example 1, but starting with di-*tert*-butyl 2-[[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](isobutyl)amino]ethyl phosphate (465 mg, 0.6 mmol) yielded compound 7 in table 1 (480 mg, 100 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.95 (s, 1H), 8.34 (s, 1H), 7.76 (m, 1H), 7.43 (s, 1H), 7.18 (m, 2H), 6.86 (s, 1H), 4.33 (m, 4H), 4.02 (s, 3H), 3.97 (s, 2H), 3.54 (m, 2H), 3.40 (m, 2H), 3.12 (d, 2H), 2.35 (m, 2H), 2.17 (m, 1H), 1.05 (d, 6H).

di-*tert*-butyl 2-[[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](isobutyl)amino]ethyl phosphate used as starting material was obtained as follows :

a) A cooled (-60 °C) solution of ethylene oxide (5.28 g, 120 mmol) in methanol (14 ml), was added slowly to a solution of isobutylamine (30.7 g, 420 mmol) in methanol (100 ml) at -65 °C under argon. The mixture was allowed to warm to ambient temperature over 14 hours, concentrated *in vacuo* and the residual oil was purified by distillation (b.p. 130 °C / 0.5 mmHg) to yield 2-(isobutylamino)ethanol (11 g, 78 % yield) :

^{1}H-NMR (DMSO d_6) : 4.40 (m, 1H), 3.42 (m, 2H), 2.50 (m, 2H), 2.30 (d, 2H), 1.63 (m, 1H), 0.85 (d, 6H).

b) An analogous reaction to that described in example 6b, but starting with 2-(isobutylamino)ethanol (936 mg, 80 mmol) and heating at 90 °C for 3.5 hours, yielded *N*-(2,3-difluorophenyl)-2-{3-[(7-{3-[(2-hydroxyethyl)(isobutyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}acetamide as an off-white solid (810 mg, 69 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.96 (s, 1H), 8.30 (s, 1H), 7.45 (m, 1H), 7.34 (s, 1H), 7.21 (m, 2H), 6.84 (s, 1H), 4.31 (m, 2H), 4.00 (s, 3H), 3.95 (s, 2H), 3.81 (m, 2H), 3.36 (m, 2H), 3.30 (m, 2H), 3.12 (m, 1H), 3.06 (m, 1H), 2.31 (m, 2H), 2.13 (m, 1H), 1.01 (d, 6H) :

MS (+ve ESI) : 584.3 $(M+H)^+$.

c) An analogous reaction to that described to that described in example 6c, but starting with *N*-(2,3-difluorophenyl)-2-{3-[(7-{3-[(2-hydroxyethyl)(isobutyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}acetamide (4.96 mg, 8.5 mmol) yielded di-*tert*-butyl 2-[[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](isobutyl)amino]ethyl phosphate (4.7 g, 71 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.96 (s, 1H), 8.30 (s, 1H), 7.74 (m, 1H), 7.34 (s, 1H), 7.19 (m, 2H), 6.84 (s, 1H), 4.30 (m, 4H), 4.00 (s, 3H), 3.94 (s, 2H), 3.54 (m, 2H), 3.39 (m, 2H), 3.12 (d, 2H), 2.32 (m, 2H), 2.14 (m, 1H), 1.45 (s, 18H), 1.02 (d, 6H) :

MS (+ve ESI) : 776.8 $(M+H)^+$.

Example 8 - Preparation of compound 8 in table 1 - 2-[[3-({4-[(5-{2-[(3,5-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](isobutyl)amino]ethyl dihydrogen phosphate

An analogous reaction to that described in example 1, but starting with di-*tert*-butyl 2-[[3-({4-[(5-{2-[(3,5-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](isobutyl)amino]ethyl phosphate (325 mg, 0.42 mmol) yielded compound 8 in table 1 (315 mg, 98 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.95 (s, 1H), 8.32 (s, 1H), 7.39 (d, 1H), 7.38 (s, 1H), 7.36 (d, 1H), 6.91 (t, 1H), 6.84 (s, 1H), 4.30 (m, 2H), 4.01 (s, 3H), 3.87 (s, 2H), 3.53 (m, 2H), 3.39 (m, 2H), 3.11 (d, 1H), 2.32 (m, 2H), 2.14 (m, 1H), 1.02 (d, 6H) :

MS (+ve ESI) : 664.3 $(M+H)^+$.

di-*tert*-butyl 2-[[3-({4-[(5-{2-[(3,5-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](isobutyl)amino]ethyl phosphate used as starting material was obtained as follows :

a) 2-(3-{[7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-5-yl)-*N*-(3,5-difluorophenyl)acetamide (2.0 g, 4.0 mmol) in 1-methyl-2-pyrrolidinone (20 ml), potassium iodide (1.33 g, 8.0 mmol) was reacted with 2-(isobutylamino)ethanol (1.88 g, 16 mmol) under argon, at 60 °C for 8 hours. The solvent was evaporated *in vacuo*, and the residue was purified by chromatography on silica gel, eluting with dichloromethane / methanol (95:5) to dichloromethane / methanol / ammonia (7.0 N) (95:5:1) to yield *N*-(3,5-difluorophenyl)-2-{3-[(7-{3-[(2-hydroxyethyl)(isobutyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}acetamide (1.05 g, 45 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.95 (s, 1H), 8.29 (s, 1H), 7.35 (d, 2H), 7.34 (s, 1H), 6.92 (t, 1H), 6.83 (s, 1H), 4.30 (m, 2H), 4.00 (s, 3H), 3.86 (s, 2H), 3.82 (t, 2H), 3.89 (m, 2H), 3.29 (m, 2H), 2.17-2.98 (m, 2H), 2.30 (m, 2H), 2.13 (m, 1H), 1.01 (d, 6H) :

MS (+ve ESI) : 584.3 $(M+H)^+$.

b) Di-*tert*-butyl-diethylphosphoramidite (1.25 ml, 4.18 mmol) was slowly added to a solution of *N*-(3,5-difluorophenyl)-2-{3-[(7-{3-[(2-hydroxyethyl)(isobutyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}acetamide (1.03 g, 1.73 mmol) in dimethylformamide (6 ml) in the presence of tetrazole (431 mg, 6.16 mmol). The mixture was stirred at ambient temperature for 2 hours before dichloromethane (30 ml) was added. The resulting mixture was washed with a saturated solution of sodium bicarbonate (15 ml), the aqueous phase was extracted with dichloromethane (3 x 25 ml), dried and concentrated *in*

vacuo. The crude product was dissolved in tetrahydrofuran (25 ml), cooled to 0 °C and hydrogen peroxide (30% w/w, 0.40 ml, 3.9 mmol) was slowly added to the solution. The reaction was stirred for 2 hours at ambient temperature, cooled to 0 °C, and treated with a solution of sodium metabisulphite (1.08 g, 5.7 mmol) in water (2 ml). The mixture was stirred for 0.5 hour at ambient temperature, diluted with ethyl acetate (30 ml), washed with aqueous sodium bicarbonate solution (15 ml) and extracted twice with ethyl acetate (20 ml) Solvent evaporation *in vacuo* followed by purification by chromatography on silica gel, eluting with dichloromethane / methanol (98:2) to dichloromethane / methanol / ammonia (7.0 N) (95:5:1) yielded di-*tert*-butyl 2-[[3-({4-[(5-{2-[(3,5-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](isobutyl)amino]ethyl phosphate (335 mg, 25 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 12.35 (s, 1H), 10.64 (s, 1H), 10.16 (s, 1H), 8.45 (s, 1H), 7.99 (s, 1H), 7.36 (d, 2H), 7.13 (s, 1H), 6.94 (t, 1H), 6.84 (s, 1H), 4.19 (t, 2H), 3.95 (s, 3H), 3.87 (q, 2H), 3.79 (s, 2H), 2.65 (m, 4H), 2.21 (d, 2H), 1.91 (m, 2H), 1.70 (m, 1H), 1.39 (s, 18H), 0.83 (d, 6H) :

MS (+ve ESI) : 776.4 $(M+H)^+$.

Example 9 - Preparation of compound 9 in table 1 - 2-[[3-({4-[(5-{2-[(3,5-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](propyl)amino]ethyl dihydrogen phosphate

An analogous reaction to that described in example 1 but starting with di-*tert*-butyl 2-[[3-({4-[(5-{2-[(3,5-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](propyl)amino]ethyl phosphate (510 mg, 0.67 mmol) yielded compound 9 in table 1 (503 mg, 42 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.94 (s, 1H), 8.31 (s, 1H), 7.38 (d, 1H), 7.37 (s, 2H), 7.36 (d, 1H), 6.92 (t, 1H), 6.83 (s, 1H), 4.30 (t, 2H), 4.24 (t, 2H), 4.00 (s, 3H), 3.87 (s, 2H), 3.49 (t, 2H), 3.36 (t, 2H), 3.18 (t, 2H), 2.26-2.36 (m, 2H), 1.68-1.79 (m, 2H), 0.94 (t, 3H) :

MS (+ve ESI) : 649.9 $(M+H)^+$.

di-*tert*-butyl 2-[[3-({4-[(5-{2-[(3,5-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](propyl)amino]ethyl phosphate used as starting was obtained as follows :

a) An analogous reaction to that described in example 8a, but starting with 2-(propylamino)ethanol (1.83 ml, 16 mmol) yielded *N*-(3,5-difluorophenyl)-2-{3-[(7-{3-[(2-

hydroxyethyl)(propyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}acetamide (900 mg, 39 % yield) :

^{1}H-NMR (DMSO d_6) : 10.63 (s, 1H), 10.17 (s, 1H), 8.46 (s, 1H), 8.00 (s, 1H), 7.36 (d, 2H), 7.14 (s, 1H), 6.94 (t, 1H), 6.85 (s, 1H), 4.35 (br s, 1H), 4.20 (t, 2H), 3.95 (s, 3H), 3.79 (s, 2H), 3.46 (m, 2H), 2.63 (m, 2H), 2.52 (m, 2H), 2.42 (m, 2H), 1.92 (m, 2H), 1.42 (m, 2H), 0.83 (t, 3H) :

MS (+ve ESI) : 570.3 $(M+H)^+$.

b) An analogous reaction to that described in example 8b, but starting with *N*-(3,5-difluorophenyl)-2-{3-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}acetamide (880 mg, 1.54 mmol) yielded di-*tert*-butyl 2-[[3-({4-[(5-{2-[(3,5-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](propyl)amino]ethyl phosphate (525 mg, 45 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 12.35 (s, 1H), 10.63 (s, 1H), 10.16 (s, 1H), 8.45 (s, 1H), 7.99 (s, 1H), 7.37 (d, 1H), 7.34 (d, 1H), 7.13 (s, 1H), 6.94 (t, 1H), 6.84 (s, 1H), 4.17 (t, 2H), 3.94 (s, 3H), 3.87 (q, 2H), 3.79 (s, 2H), 2.67 (t, 2H), 2.63 (t, 2H), 2.43 (t, 2H), 1.91 (t, 2H), 1.39 (s, 18H), 0.83 (t, 3H) :

MS (+ve ESI) : 762.6 $(M+H)^+$.

Example 10 - Preparation of compound 10 in table 1 - 2-[[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](isobutyl)amino]ethyl dihydrogen phosphate

An analogous reaction to that described in example 1, but starting with di-*tert*-butyl 2-[[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](isobutyl)amino]ethyl phosphate (450 mg, 0.59 mmol) yielded compound 10 in table 1 (420 mg, 99 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.90 (s, 1H), 8.30 (s, 1H), 7.64 (m, 1H), 7.36 (m, 3H), 6.85 (m, 2H), 4.30 (m, 4H), 4.00 (s, 3H), 3.86 (s, 2H), 3.53 (m, 2H), 3.37 (m, 2H), 3.09 (m, 2H), 2.34 (m, 2H), 2.14 (m, 1H), 1.05 (m, 6H) :

MS (+ve ESI) : 646.6 $(M+H)^+$.

di-*tert*-butyl 2-[[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](isobutyl)amino]ethyl phosphate used as starting material was obtained as follows :

a) An analogous reaction to that described in example 5a, but starting with 2-(isobutyl amino)ethanol (181 mg, 1.55 mmol) yielded *N*-(3-fluorophenyl)-2-{3-[(7-{3-[(2-hydroxyethyl)(isobutyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}acetamide (101 mg, 57 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.96 (s, 1H), 8.30 (s, 1H), 7.63 (d, 1H), 7.32-7.41 (m, 2H), 7.34 (s, 1H), 6.90 (t, 1H), 6.83 (s, 1H), 4.30 (t, 2H), 4.00 (s, 3H), 3.84 (s, 2H), 3.80 (t, 2H), 3.37 (t, 2H), 3.28 (t, 2H), 3.15-3.00 (m, 2H), 2.29 (m, 2H), 2.12 (m, 2H), 1.00 (d, 6H) :
MS (+ve ESI) : 566.3 $(M+H)^+$.

b) An analogous reaction to that described in example 5b, but starting with *N*-(3-fluorophenyl)-2-{3-[(7-{3-[(2-hydroxyethyl)(isobutyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}acetamide (565 mg, 1 mmol) yielded di-*tert*-butyl 2-[[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](isobutyl)amino]ethyl phosphate (420 mg, 55 % yield) :
^{1}H-NMR (DMSO d_6, TFA) : 8.37 (s, 1H), 7.88 (s, 1H), 7.55 (m, 1H), 7.26 (m, 2H), 7.04 (s, 1H), 6.81 (m, 2H), 4.09 (t, 2H), 3.82 (s, 3H), 3.76 (m, 2H), 3.67 (m, 2H), 2.57 (m, 4H), 2.11 (m, 2H), 1.82 (m, 2H), 1.60 (m, 1H), 1.29 (s, 18H), 0.74 (d, 6H) :
MS (+ve ESI) : 758.5 $(M+H)^+$.

Example 11 - Preparation of compound 11 in table 1 - 2-{(2,2-dimethylpropyl)[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate

An analogous reaction to that described in example 1, but starting with di-*tert*-butyl 2-{(2,2-dimethylpropyl)[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate (350 mg, 0.45 mmol) yielded compound 11 in table 1 (325 mg, 100 % yield) :
^{1}H-NMR (DMSO d_6, TFA) : 8.94 (s, 1H), 8.3 (s, 1H), 7.63 (d, 1H), 7.36 (s, 1H), 7.34 (m, 2H), 6.88 (m, 1H), 6.82 (s, 1H), 4.30 (m, 4H), 3.99 (s, 3H), 3.84 (s, 2H), 3.54 (m, 2H), 3.38 (m, 2H), 3.19 (m, 2H), 2.37 (m, 2H), 1.09 (s, 9H) :
MS (+ve ESI) : 660.4 $(M+H)^+$.

di-*tert*-butyl 2-{(2,2-dimethylpropyl)[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate used as starting material was obtained as follows :

a) Ethylene oxide (2.5 ml, 5.0 mmol) cooled to –20 °C was slowly added to a solution of (2,2-dimethylpropyl)amine (13 g, 150 mmol) in methanol (15 ml) at –30 °C under argon. The mixture was stirred at ambient temperature for 16 hours. The solvent was evaporated *in vacuo*, and the residue was purified by distillation (b.p. 132°C / 9 mmHg) to yield 2-((2,2-dimethylpropyl)amino)ethanol (6.4 g, 97 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 3.70 (m, 2H), 3.02 (m, 2H), 2.81 (m, 2H), 0.98 (s, 9H).

b) An analogous reaction to that described in example 5a, but starting with 2-(2,2-dimethylpropyl)amino)ethanol (203 mg, 1.55 mmol) yielded 2-{3-[(7-{3-[(2,2-dimethylpropyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}-*N*-(3-fluorophenyl)acetamide (111 mg, 61 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.96 (s, 1H), 8.30 (s, 1H), 7.64 (d, 1H), 7.32-7.41 (m, 2H), 7.34 (s, 1H), 6.90 (t, 1H), 6.83 (s, 1H), 4.31 (t, 2H), 3.99 (s, 3H), 3.84 (s, 2H), 3.83 (t, 2H), 3.42 (t, 2H), 3.32 (t, 2H), 3.20 (dd, 2H), 2.35 (m, 2H), 1.07 (s, 9H) :

MS (+ve ESI) : 580.3 $(M+H)^+$.

c) An analogous reaction to that described in example 5b, but starting with 2-{3-[(7-{3-[(2,2-dimethylpropyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}-*N*-(3-fluorophenyl)acetamide (1.33 g, 2.3 mmol) yielded di-*tert*-butyl 2-{(2,2-dimethylpropyl)[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate (620 mg, 40 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.95 (s, 1H), 8.3 (s, 1H), 7.64 (d, 1H), 7.28-7.40 (m, 2H), 7.34 (s, 1H), 6.88 (m, 1H), 6.84 (s, 1H), 4.31 (m, 4H), 4.00 (s, 3H), 3.85 (s, 2H), 3.56 (m, 2H), 3.39 (m, 2H), 3.21 (m, 2H), 2.32 (m, 2H), 1.43 (s, 9H), 1.10 (s, 9H) :

MS (+ve ESI) : 716.4 $(M+H)^+$.

Example 12 - Preparation of compound 12 in table 1 - 1-[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]piperidin-3-yl dihydrogen phosphate

An analogous reaction to that described in example 1, but starting with di-*tert*-butyl 1-[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]piperidin-3-yl phosphate (540 mg, 0.72 mmol) yielded compound 12 in table 1 (500 mg, 98 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.92 (s, 1H), 8.28 (s, 1H), 7.62 (d, 1H), 7.32 (m, 3H), 6.82 (m, 2H), 4.45-4.66 (m, 2H), 4.27 (m, 2H), 3.99 (s, 3H), 3.84 (s, 2H), 3.55 (m, 2H), 3.30 (m, 2H), 3.00 (m, 2H), 2.30 (m, 2H), 2.05 (m, 2H), 1.65 (m, 2H) :

MS (+ve ESI) : 630.2 $(M+H)^+$.

di-*tert*-butyl 1-[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]piperidin-3-yl phosphate used starting material was obtained as follows :

a) An analogous reaction to that described in example 5a, but starting with piperidin-3-ol (101 mg, 1 mmol) yielded *N*-(3-fluorophenyl)-2-[3-({7-[3-(3-hydroxypiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-5-yl]acetamide (65 mg, 47 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.96 (s, 1H), 8.29 (s, 1H), 7.62 (d, 1H), 7.38 (m, 2H), 7.34 (m, 2H), 7.34 (s, 1H), 6.90 (m, 1H), 6.84 (s, 1H), 4.28 (m, 2H), 4.10 (m, 1H), 4.00 (s, 3H), 3.85 (s, 2H), 2.80-3.50 (m, 6H), 1.30-2.40 (m, 6H) :

MS (+ve ESI) : 550.6 $(M+H)^+$.

b) An analogous reaction to that described in example 5b, but starting with *N*-(3-fluorophenyl)-2-[3-({7-[3-(3-hydroxypiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-5-yl]acetamide (604 mg, 1.1 mmol) yielded di-*tert*-butyl 1-[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]piperidin-3-yl phosphate (550 mg, 67 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.38 (s, 1H), 7.90 (s, 1H), 7.55 (d, 1H), 7.30 (m, 2H), 7.06 (s, 1H), 6.80 (m, 2H), 4.09 (m, 3H), 3.86 (s, 3H), 3.68 (s, 2H), 2.80 (m, 1H), 2.55 (m, 1H), 2.03 (m, 2H), 1.87 (m, 3H), 1.60 (m, 1H), 1.35 (m, 22H) :

MS (+ve ESI) : 742.5 $(M+H)^+$.

Example 13 - Preparation of compound 13 in table 1 - {(2*R*)-1-[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate

An analogous reaction to that described in example 1, but starting with di-*tert*-butyl {(2*R*)-1-[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate (445 mg, 0.59 mmol) yielded compound 13 in table 1 (440 mg, 94 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.94 (s, 1H), 8.31 (s, 1H), 7.73 (m, 1H), 7.40 (s, 1H), 7.19 (m, 2H), 6.83 (s, 1H), 4.31 (t, 2H), 4.20 (m, 2H), 4.01 (s, 3H), 3.94 (s, 2H), 3.82 (m, 1H), 3.70 (m, 1H), 3.60 (m, 1H), 3.31 (m, 1H), 3.23 (m, 1H), 2.32 (m, 2H), 2.19 (m, 1H), 2.04 (m, 1H), 1.95 (m, 1H), 1.85 (m, 1H) :

MS (+ve ESI) : 648.3 $(M+H)^+$.

di-*tert*-butyl {(2*R*)-1-[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate used as starting material was obtained as follows :

a) An analogous reaction to that described in example 6b, but starting with (2R)-pyrrolidin-2-ylmethanol (101 mg, 1 mmol) yielded *N*-(2,3-difluorophenyl)-2-{3-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}acetamide (134 mg, 79 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.95 (s, 1H), 8.29 (s, 1H), 7.75 (m, 1H), 7.32 (s, 1H), 7.16 (m, 2H), 6.84 (s, 1H), 4.30 (m, 2H), 4.00 (s, 3H), 3.94 (s, 2H), 3.70-3.85 (m, 1H), 3.52-3.70 (m, 4H), 3.15-3.30 (m, 2H), 2.25-2.35 (m, 2H), 1.75-2.20 (m, 4H) :

MS ES^+ : 568.2 $(M+H)^+$

MS (+ve ESI) : 568.2 $(M+H)^+$.

b) An analogous reaction to that described in example 6c, but starting with *N*-(2,3-difluorophenyl)-2-{3-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}acetamide (1.1 g, 1.9 mmol) yielded di-*tert*-butyl {(2*R*)-1-[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate (453 mg, 31 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 10.24 (s, 1H), 10.15 (s, 1H), 8.44 (s, 1H), 7.98 (s, 1H), 7.72 (t, 1H), 7.19 (m, 2H), 7.13 (s, 1H), 6.83 (s, 1H), 4.17 (br s, 2H), 3.93 (s, 3H), 3.85 (s, 1H), 3.77 (m, 1H), 3.56 (t, 1H), 3.54 (t, 1H), 3.08 (t, 1H), 2.94 (m, 1H), 2.66 (m, 1H), 2.47 (m, 1H), 2.20 (q, 1H), 1.94 (m, 2H), 1.86 (m, 1H), 1.69 (m, 2H), 1.60 (m, 1H), 1.37 (s, 9H), 1.36 (s, 9H) :

MS (+ve ESI) : 758.5 $(M+H)^+$.

Example 14 - Preparation of compound 14 in table 1 - 2-[[3-({4-[(5-{2-[(3,5-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](prop-2-yn-1-yl)amino]ethyl dihydrogen phosphate

An analogous reaction to that described in example 1, but starting with di-*tert*-butyl 2-[[3-({4-[(5-{2-[(3,5-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](prop-2-yn-1-yl)amino]ethyl phosphate (400 mg, 0.53 mmol) yielded compound 14 in table 1 (290 mg, 77 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.94 (s, 1H), 8.34 (s, 1H), 7.42 (m, 3H), 6.89 (m, 2H), 4.37 (m, 6H), 4.04 (s, 3H), 3.92 (s, 2H), 3.87 (s, 1H), 3.57 (m, 2H), 3.47 (m, 2H), 2.39 (m, 2H) :

MS (+ve ESI) : 646.4 $(M+H)^+$.

di-*tert*-butyl 2-[[3-({4-[(5-{2-[(3,5-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](prop-2-yn-1-yl)amino]ethyl phosphate used as starting material was obtained as follows :

a) A cooled (–40 °C) solution of ethylene oxide (3.3 g, 75 mmol) in methanol (10 ml) was slowly added to a solution of propargylamine (16.5 g, 300 mmol) in methanol (60 ml) cooled to –65 ° C under argon. The mixture was allowed to warm to ambient temperature over 16 hours, the solvent was evaporated *in vacuo*, and the residue was purified by distillation to yield 2-(prop-2-yn-1-ylamino)ethanol (5.0 g, 67 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 3.91 (m, 2H), 3.65 (m, 3H), 3.06 (m, 2H).

b) An analogous reaction to that described in example 8a, but starting with 2-(prop-2-yn-1-ylamino)ethanol (99 mg, 1 mmol) and heating at 105 °C for 12 hours yielded *N*-(3,5-difluorophenyl)-2-{3-[(7-{3-[(2-hydroxyethyl)(prop-2-yn-1-yl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}acetamide (50 mg, 31 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.95 (s, 1H), 8.29 (s, 1H), 7.34 (m, 2H), 7.31 (s, 1H), 6.91 (m, 1H), 6.83 (s, 1H), 4.29 (m, 4H), 4.00 (s, 3H), 3.89 (m, 1H), 3.86 (s, 2H), 3.80 (m, 2H), 3.43 (m, 2H), 3.36 (m, 2H), 2.30 (m, 2H) :

MS (+ve ESI) : 566.2 $(M+H)^+$.

c) An analogous reaction to that described in example 8b, but starting with *N*-(3,5-difluorophenyl)-2-{3-[(7-{3-[(2-hydroxyethyl)(prop-2-yn-1-yl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}acetamide (734 mg, 1.3 mmol) yielded di-*tert*-butyl 2-[[3-({4-[(5-{2-[(3,5-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](prop-2-yn-1-yl)amino]ethyl phosphate (400 mg, 41 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.51 (s, 1H), 7.99 (s, 1H), 7.35 (m, 2H), 7.28 (s, 1H), 6.93 (m, 1H), 6.72 (s, 1H), 4.21 (m, 2H), 3.95 (m, 5H), 3.75 (m, 2H), 3.60 (m, 2H), 3.28 (s, 1H), 2.85 (m, 2H), 2.79 (m, 2H), 1.97 (m, 2H), 1.37 (s, 9H).

Example 15 - Preparation of compound 15 in table 1 - 2-[[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](isopropyl)amino]ethyl dihydrogen phosphate

An analogous reaction to that described in example 1, but starting with di-*tert*-butyl 2-[[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](isopropyl)amino]ethyl phosphate (450 mg, 0.59 mmol) yielded compound 15 in table 1 (405 mg, 95 % yield) :

^{1}H-NMR (DMSO d_6) : 8.90 (s, 1H), 8.32 (s, 1H), 7.69 (m, 1H), 7.51 (s, 1H), 7.21 (m, 2H), 6.81 (s, 1H), 4.33 (m, 2H), 4.26 (m, 2H), 4.00 (s, 3H), 3.92 (s, 2H), 3.72 (m, 1H), 3.40 (m, 2H), 3.29 (m, 2H), 2.32 (m, 2H), 1.31 (m, 6H) :

MS (+ve ESI) : 650.3 $(M+H)^+$.

di-*tert*-butyl 2-[[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](isopropyl)amino]ethyl phosphate used as starting material was obtained as follows :

a) An analogous reaction to that described in example 6b, but starting with 2-(isopropylamino)ethanol (103 mg, 1 mmol) yielded *N*-(2,3-difluorophenyl)-2-{3-[(7-{3-[(2-hydroxyethyl)(isopropyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}acetamide (84 mg, 49 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.97 (s, 1H), 8.33 (s, 1H), 7.79 (m, 1H), 7.35 (s, 1H), 7.18 (m, 2H), 6.88 (s, 1H), 4.34 (t, 2H), 4.03 (s, 3H), 3.98 (s, 2H), 3.81 (m, 3H), 3.40 (m, 3H), 3.20 (m, 1H), 2.35 (m, 2H), 1.33 (m, 6H) :

MS (+ve ESI) : 570.2 $(M+H)^+$.

b) An analogous reaction to that described in example 6c, but starting with *N*-(2,3-difluorophenyl)-2-{3-[(7-{3-[(2-hydroxyethyl)(isopropyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}acetamide (650 mg, 1.14 mmol) yielded di-*tert*-butyl 2-[[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](isopropyl)amino]ethyl phosphate (520 mg, 60 % yield) :

^{1}H-NMR (DMSO d_6) : 8.44 (s, 1H), 7.98 (s, 1H), 7.73 (m, 1H), 7.19 (m, 2H), 7.12 (s, 1H), 6.83 (s, 1H), 4.16 (t, 2H), 3.93 (s, 3H), 3.85 (s, 2H), 3.77 (m, 2H), 2.90 (m, 1H), 2.60 (m, 4H), 1.86 (m, 2H), 1.36 (s, 18H), 0.94 (m, 6H) :

MS (+ve ESI) : 762.7 $(M+H)^+$.

Example 16 - Preparation of compound 16 in table 1 - 2-[[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](prop-2-yn-1-yl)amino]ethyl dihydrogen phosphate

An analogous reaction to that described in example 1, but starting with di-*tert*-butyl 2-[[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](prop-2-yn-1-yl)amino]ethyl phosphate (630 mg, 0.84 mmol) yielded compound 16 in table 1 ((540 mg, 86 % yield) :

^{1}H-NMR (DMSO d_6, AcOD) : 8.89 (s, 1H), 8.29 (m, 1H), 7.70 (m, 1H), 7.37 (m, 1H), 7.16 (m, 2H), 6.81 (m, 1H), 4.29 (m, 6H), 3.99 (m, 3H), 3.92 (m, 2H), 3.82 (m, 1H), 3.52 (m, 2H), 3.43 (m, 2H), 2.32 (m, 2H) :

MS (+ve ESI) : 646.3 $(M+H)^+$.

di-*tert*-butyl 2-[[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](prop-2-yn-1-yl)amino]ethyl phosphate used as starting material was obtained as follows :

a) An analogous reaction to that described in example 6b, but starting with 2-(prop-2-yn-1-ylamino)ethanol (99 mg, 1 mmol) yielded *N*-(2,3-difluorophenyl)-2-{3-[(7-{3-[(2-hydroxyethyl)(prop-2-yn-1-yl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}acetamide (128 mg, 75 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.95 (s, 1H), 8.29 (s, 1H), 7.74 (m, 1H), 7.31 (s, 1H), 7.18 (m, 2H), 6.83 (s, 1H), 4.30 (m, 4H), 4.00 (s, 3H), 3.94 (s, 2H), 3.87 (m, 1H), 3.80 (m, 2H), 3.44 (m, 2H), 3.35 (m, 2H), 2.30 (m, 2H) :

MS (+ve ESI) : 566.2 $(M+H)^+$.

b) An analogous reaction to that described in example 6c, but starting with *N*-(2,3-difluorophenyl)-2-{3-[(7-{3-[(2-hydroxyethyl)(prop-2-yn-1-yl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}acetamide (680 mg, 1.2 mmol) yielded di-*tert*-butyl 2-[[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](prop-2-yn-1-yl)amino]ethyl phosphate (630 mg, 70 % yield) :

^{1}H-NMR (DMSO d_6) : 8.45 (s, 1H), 7.98 (s, 1H), 7.72 (m, 1H), 7.17 (m, 3H), 6.83 (s, 1H), 4.16 (m, 2H), 3.85 (m, 7H), 3.45 (m, 2H), 3.13 (m, 1H), 2.69 (m, 4H), 1.90 (m, 2H), 1.35 (m, 18H) :

MS (+ve ESI) : 758.5 $(M+H)^+$.

Example 17 - Preparation of compound 17 in table 1 - 2-[[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](2-methoxyethyl)amino]ethyl dihydrogen phosphate

An analogous reaction to that described in example 1, but starting with di-*tert*-butyl 2-[[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](2-methoxyethyl)amino]ethyl phosphate (500 mg, 0.64 mmol) yielded compound 17 in table 1 (450 mg, 94 % yield) :

^{1}H-NMR (DMSO d_6, AcOD) : 8.91 (s, 1H), 8.33 (s, 1H), 7.74 (m, 1H), 7.43 (s, 1H), 7.18 (m, 2H), 6.85 (s, 1H), 4.32 (m, 4H), 4.02 (s, 3H), 3.96 (s, 2H), 3.77 (m, 2H), 3.56 (m, 2H), 3.49 (m, 2H), 3.44 (m, 2H), 3.34 (s, 3H), 2.34 (m, 2H) :

MS (+ve ESI) : 666.2 $(M+H)^+$.

di-*tert*-butyl 2-[[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](2-methoxyethyl)amino]ethyl phosphate used as starting material was obtained as follows :

a) An analogous reaction to that described in example 6b, but starting with 2-((2-methoxyethyl)amino)ethanol (119 mg, 1 mmol – prepared according to A.A. Santilli *et al, J. Heterocycl. Chem.* **1972**, *9*, 309-13) yielded *N*-(2,3-difluorophenyl)-2-{3-[(7-{3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}acetamide (124 mg, 71 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.97 (s, 1H), 8.31 (s, 1H), 7.76 (m, 1H), 7.33 (s, 1H), 7.19 (m, 2H), 6.85 (s, 1H), 4.31 (t, 2H), 4.02 (s, 3H), 3.95 (s, 2H), 3.80 (t, 2H), 3.73 (t, 2H), 3.45 (m, 4H), 3.36 (m, 5H), 2.31 (m, 2H) :

MS (+ve ESI) : 586.2 $(M+H)^+$.

b) An analogous reaction to that described in example 6c, but starting with *N*-(2,3-difluorophenyl)-2-{3-[(7-{3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}acetamide (800 mg, 1.4 mmol) yielded di-*tert*-butyl 2-[[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](2-methoxyethyl)amino]ethyl (560 mg, 53 % yield) :

^{1}H-NMR (DMSO d_6) : 8.44 (s, 1H), 7.99 (s, 1H), 7.72 (m, 1H), 7.20 (m, 2H), 7.12 (s, 1H), 6.84 (s, 1H), 4.16 (t, 2H), 3.93 (t, 3H), 3.85 (m, 4H), 3.38 (m, 2H), 3.20 (s, 3H), 2.74 (m, 2H), 2.67 (m, 4H), 1.90 (m, 2H), 1.39 (m, 18H) :

MS (+ve ESI) : 778.6 $(M+H)^+$.

Example 18 - Preparation of compound 18 in table 1 - 2-{[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate

An analogous reaction to that described in example 1, but starting with di-*tert*-butyl 2-{[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate (729 mg, 1.04 mmol) yielded compound 18 in table 1 (505 mg, 72 % yield) :

^{1}H-NMR (DMSO d_6, AcOD) : 8.85 (s, 1H), 8.25 (s, 1H), 7.60 (d, 1H), 7.33 (m, 3H), 6.83 (m, 1H), 6.80 (s, 1H), 4.27 (m, 2H), 4.15 (m, 2H), 3.97 (s, 3H), 3.83 (s, 2H), 3.26 (m, 2H), 3.15 (m, 2H), 2.24 (m, 2H) :

MS (+ve ESI) : 590.1 $(M+H)^+$.

di-*tert*-butyl 2-{[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate used as starting material was obtained as follows :

a) An analogous reaction to that described in example 5a, but starting with 2-(cyclopropylamino)ethanol (156 mg, 1.55 mmol) yielded 2-{3-[(7-{3-[cyclopropyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}-*N*-(3-fluorophenyl)acetamide (22 mg, 13 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.97 (s, 1H), 8.31 (s, 1H), 7.65 (d, 1H), 7.33-7.42 (m, 2H), 7.37 (s, 1H), 6.92 (t, 1H), 6.85 (s, 1H), 4.33 (m, 2H), 4.02 (s, 3H), 3.86 (s, 2H), 3.79 (t, 2H), 3.48 (m, 2H), 3.42 (t, 2H), 2.97 (m, 1H), 2.36 (m, 2H), 1.04 (m, 2H), 0.94 (m, 2H) :

MS (+ve ESI) : 550.2 $(M+H)^+$.

b) An analogous reaction to that described in example 5b, but starting with 2-{3-[(7-{3-[cyclopropyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}-*N*-(3-fluorophenyl)acetamide (1.1 g, 2.0 mmol) yielded a mixture of di-*tert*-butyl 2-{cyclopropyl[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate (150 mg, 10 % yield) together with di-*tert*-butyl 2-{[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-

pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate (730 mg, 52 % yield) which was used in the next step :

^{1}H-NMR (DMSO d_6, TFA) : 8.97 (s, 1H), 8.32 (s, 1H), 7.78 (d, 1H), 7.36 (m, 2H), 7.34 (s, 1H), 6.87 (m, 2H), 4.33 (m, 2H), 4.16 (m, 2H), 4.03 (s, 3H), 3.88 (s, 2H), 3.33 (m, 2H), 3.24 (m, 2H), 2.38 (m, 2H), 1.47 (s, 18H) :

MS (+ve ESI) : 702.5 $(M+H)^+$.

Example 19 - Preparation of compound 19 in table 1 - 2-{(cyclobutylmethyl)[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate

An analogous reaction to that described in example 1, but starting with di-*tert*-butyl 2-{(cyclobutylmethyl)[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate (400 mg, 0.508 mmol) yielded compound 19 in table 1 (365 mg, 96 % yield) :

^{1}H-NMR (DMSO d_6, AcOD) : 8.92 (s, 1H), 8.33 (s, 1H), 7.71 (m, 1H), 7.44 (s, 1H), 7.19 (m, 2H), 6.82 (s, 1H), 4.30 (m, 4H), 4.00 (s, 3H), 3.94 (s, 2H), 3.42 (m, 2H), 3.29 (m, 4H), 2.82 (m, 1H), 2.31 (m, 2H), 2.13 (m, 2H), 1.87 (m, 4H) :

MS (+ve ESI) : 676.4 $(M+H)^+$.

di-*tert*-butyl 2-{(cyclobutylmethyl)[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate used as starting material was obtained as follows :

a) Cyclobutane carbonyl chloride (5 ml, 43.8 mmol) was slowly added to a solution of ethyl glycinate (5.86 g, 42 mmol) in dichloromethane (100 ml) and triethylamine (14.6 ml, 105 mmol) at 0 °C. The mixture was then stirred at ambient temperature for 14 hours. The reaction mixture was washed with a dilute hydrochloric acid (1.0 N), the organic phase was separated, dried and evaporated *in vacuo* to give a yellow solid. Recrystallisation from dichloromethane / petroleum ether yielded ethyl N-(cyclobutylcarbonyl)glycinate as a white solid (7.78 g, 100 % yield) :

^{1}H-NMR (DMSO d_6) : 8.08 (t, 1H), 4.09 (q, 2H), 3.79 (s, 2H), 3.07 (m, 1H), 2.00-2.18 (m, 4H), 1.89 (m, 1H), 1.78 (m, 1H), 1.20 (t, 3H).

b) Ethyl N-(cyclobutylcarbonyl)glycinate (7.6 g, 41 mmol) in tetrahydrofuran (40 ml) was added to a solution of diborane (100 ml of a 1.0 N solution in tetrahydrofuran, 100 mmol) and heated at 60 °C for 24 hours. Additional diborane (20 ml of a 1.0 N solution in

tetrahydrofuran, 20 mmol) was added to the mixture and heating was carried out for a further 8 hours. Methanol (20 ml) was added cautiously and the reaction stirred for 30 minutes at ambient temperature before slow addition of hydrochloric acid (6 ml of a 6.0 N solution). The reaction was concentrated *in vacuo*, dichloromethane was added and the solid material removed by suction filtration. The organic filtrate was dried, concentrated *in vacuo* and purified by chromatography on silica gel, eluting with dichloromethane / methanol (96:4) to dichloromethane / methanol / ammonia (7.0N) (94:5:1) to yield 2-((cyclobutylmethyl)amino)ethanol (4.16 g, 78 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.38 (br s, 1H), 3.65 (t, 2H), 2.98 (m, 4H), 2.62 (m, 2H), 2.06 (m, 2H), 1.72-1.94 (m, 4H).

c) An analogous reaction to that described in example 6b, but starting with 2-((cyclobutylmethyl)amino)ethanol (129 mg, 1 mmol) yielded 2-{3-[(7-{3-[(cyclobutylmethyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}-*N*-(2,3-difluorophenyl)acetamide (134 mg, 75 % yield) :

^{1}H-NMR (DMSO d_6) : 8.49 (s, 1H), 8.00 (s, 1H), 7.74 (m, 1H), 7.15-7.30 (m, 3H), 6.75 (m, 1H), 4.25 (m, 2H), 3.96 (s, 3H), 3.86 (s, 2H), 3.60-3.80 (m, 2H), 3.30-3.40 (m, 4H), 2.50-2.80 (m, 4H), 1.60-2.40 (m, 7H) :

MS (+ve ESI) : 596.2 $(M+H)^+$.

d) An analogous reaction to that described in example 6c, but starting with 2-{3-[(7-{3-[(cyclobutylmethyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}-*N*-(2,3-difluorophenyl)acetamide (773 mg, 1.3 mmol) yielded di-*tert*-butyl 2-{(cyclobutylmethyl)[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate (400 mg, 40 % yield) :

^{1}H-NMR (DMSO d_6) : 8.45 (s, 1H), 7.99 (s, 1H), 7.72 (m, 1H), 7.20 (m, 3H), 6.83 (s, 1H), 4.15 (s, 2H), 3.94 (s, 3H), 3.85 (m, 4H), 2.60 (m, 4H), 2.47 (m, 3H), 1.88 (m, 4H), 1.75 (m, 2H), 1.60 (m, 2H), 1.36 (s, 18H) :

MS (+ve ESI) : 788.8 $(M+H)^+$.

Example 20 - Preparation of compound 20 in table 1 - 2-[[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](3,3,3-trifluoropropyl)amino]ethyl dihydrogen phosphate

An analogous reaction to that described in example 1, but starting with di-*tert*-butyl 2-[[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](3,3,3-trifluoropropyl)amino]ethyl phosphate (450 mg, 0.56 mmol) yielded compound 20 in table 1 (405 mg, 46 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.95 (s, 1H), 8.32 (s, 1H), 7.65 (d, 1H), 7.39 (s, 1H), 7.36 (m, 1H), 6.89 (m, 1H), 6.83 (s, 1H), 4.31 (t, 2H), 4.27 (m, 2H), 4.01 (s, 2H), 3.86 (s, 2H), 3.57 (br s, 2H), 3.54 (m, 2H), 3.43 (t, 2H), 2.97 (m, 2H), 2.33 (m, 2H) :

MS (+ve ESI) : 686.4 $(M+H)^+$.

di-*tert*-butyl 2-[[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](3,3,3-trifluoropropyl)amino]ethyl phosphate used as starting material was obtained as follows :

a) A solution of 3-bromo-1,1,1-trifluoropropane (5.5 ml, 51.6 mmol) in dioxane (50 ml) was heated with ethanol amine (3 ml, 51.25 mmol) at 60 °C for 36 hours in the presence of potassium carbonate (14.2 g, 102 mmol). The solvent was evaporated in vacuo and the residue was purified by chromatography on silica gel, eluting with dichloromethane / methanol (95:5) to dichloromethane / methanol / ammonia (7.0 N) (95:5:1) to yield 2-((3,3,3-trifluoropropyl)amino)ethanol (4.47 g, 55 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 3.56 (t, 2H), 2.97 (t, 2H), 2.82 (t, 2H), 2.57 (m, 2H).

b) An analogous reaction to that described in example 5a, but starting with 2-((3,3,3-trifluoropropyl)amino)ethanol (221 mg, 1.55 mmol) yielded *N*-(3-fluorophenyl)-2-{3-[(7-{3-[(2-hydroxyethyl)(3,3,3-trifluoropropyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}acetamide (77 mg, 41 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.96 (s, 1H), 8.29 (s, 1H), 7.63 (d, 1H), 7.31-7.40 (m, 2H), 7.33 (s, 1H), 6.89 (t, 1H), 6.83 (s, 1H), 4.29 (t, 2H), 3.99 (s, 3H), 3.84 (s, 2H), 3.79 (t, 2H), 3.51 (m, 2H), 3.38 (m, 2H), 2.91 (m, 2H), 2.29 (m, 2H) :

MS (+ve ESI) : 606.2 $(M+H)^+$.

c) An analogous reaction to that described in example 5b, but starting with *N*-(3-fluorophenyl)-2-{3-[(7-{3-[(2-hydroxyethyl)(3,3,3-trifluoropropyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}acetamide (651 mg, 1.07 mmol) yielded di-*tert*-butyl 2-[[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-

methoxyquinazolin-7-yl}oxy)propyl](3,3,3-trifluoropropyl)amino]ethyl phosphate (455 mg, 53 % yield) :

^{1}H-NMR (DMSO d_6) : 10.45 (s, 1H), 10.15 (s, 1H), 8.44 (s, 1H), 7.98 (s, 1H), 7.62 (d, 1H), 7.35 (m, 1H), 7.33 (s, 1H), 7.13 (s, 1H), 6.89 (t, 1H), 6.82 (s, 1H), 4.16 (t, 2H), 3.93 (s, 3H), 3.87 (q, 2H), 3.76 (s, 2H), 2.73 (m, 4H), 2.66 (t, 2H), 2.42 (m, 2H), 1.90 (m, 2H), 1.37 (s, 18H) :

MS (+ve ESI) : 797.9 $(M+H)^+$.

Example 21 - Preparation of compound 21 in table 1 - 2-{allyl[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate

An analogous reaction to that described in example 1, but starting with 2-{allyl[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl di-*tert*-butyl phosphate (310 mg, 0.408 mmol) yielded compound 21 in table 1 (293 mg, 100 % yield) :

^{1}H-NMR (DMSO d_6, AcOD) : 8.92 (s, 1H), 8.32 (s, 1H), 7.70 (m, 1H), 7.43 (s, 1H), 7.19 (m, 2H), 6.82 (s, 1H), 6.05 (m, 1H), 5.63 (m, 1H), 5.56 (m, 1H), 4.30 (m, 4H), 4.00 (s, 3H), 3.93 (m, 4H), 3.45 (m, 2H), 3.33 (m, 2H), 2.33 (m, 2H) :

MS (+ve ESI) : 648.3 $(M+H)^+$.

2-{allyl[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl di-*tert*-butyl phosphate used as starting material was obtained as follows :

a) Ethylene oxide (2.5 ml, 50 mmol - cooled to –20 °C) was added to a solution of allylamine (14 g, 250 mmol) in methanol (20 ml) at –20 °C. The mixture was stirred at ambient temperature for 14 hours, the solvent was evaporated *in vacuo* and the residual oil was purified by distillation (b.p. 140 °C / 14 mmHg) to yield 2-(allylamino)ethanol (4.2 g, 84 % yield) :

^{1}H-NMR (DMSO d_6) : 5.83 (m, 1H), 5.14 (m, 1H), 5.02 (m, 1H), 3.43 (m, 2H), 3.14 (m, 2H), 2.50 (m, 2H).

b) An analogous reaction to that described in example 6b, but starting with 2-(allylamino)ethanol (101 mg, 1 mmol) yielded 2-{3-[(7-{3-[allyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}-*N*-(2,3-difluorophenyl)acetamide (99 mg, 58 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.97 (s, 1H), 8.32 (s, 1H), 7.77 (m, 1H), 7.33 (s, 1H), 7.18 (m, 2H), 6.87 (s, 1H), 6.01 (m, 1H), 5.60 (m, 2H), 4.31 (t, 2H), 4.02 (s, 3H), 3.94 (m, 4H), 3.82 (t, 2H), 3.35 (m, 4H), 2.34 (m, 2H) :

MS (+ve ESI) : 568.2 $(M+H)^+$.

c) An analogous reaction to that described in example 6c, but starting with 2-{3-[(7-{3-[allyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}-*N*-(2,3-difluorophenyl)acetamide (1.0 g, 1.76 mmol) yielded 2-{allyl[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl di-*tert*-butyl phosphate (310 mg, 23 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.97 (s, 1H), 8.30 (s, 1H), 7.75 (m, 1H), 7.32 (s, 1H), 7.20 (m, 2H), 6.85 (s, 1H), 6.00 (m, 1H), 5.74 (m, 2H), 4.30 (m, 4H), 4.01 (s, 3H), 3.95 (m, 4H), 3.50 (m, 2H), 3.37 (m, 2H), 2.30 (m, 2H), 1.45 (s, 18H) :

MS (+ve ESI) : 760.5 $(M+H)^+$.

Example 22 - Preparation of compound 22 in table 1 - 2-{cyclobutyl[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate

An analogous reaction to that described in example 1, but starting with di-*tert*-butyl 2-{cyclobutyl[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate (450 mg, 0.58 mmol) yielded compound 22 in table 1 (420 mg, 98 % yield) :

^{1}H-NMR (DMSO d_6, AcOD) : 8.91 (s, 1H), 8.31 (s, 1H), 7.72 (m, 1H), 7.42 (s, 1H), 7.20 (m, 2H), 6.82 (s, 1H), 4.28 (m, 4H), 4.00 (s, 3H), 3.94 (s, 3H), 3.35 (m, 2H), 3.25 (m, 2H), 2.41 (m, 2H), 2.25 (m, 4H), 1.70 (m, 2H) :

MS (+ve ESI) : 662.5 $(M+H)^+$.

di-*tert*-butyl 2-{cyclobutyl[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate used as starting material was obtained as follows :

a) An analogous reaction to that described in example 6b, but starting with 2-(cyclobutylamino)ethanol (117 mg, 1 mmol – prepared according to D.F. Morrow *et al*, *J. Med. Chem.* **1973**, *16*, 736-9.) and potassium iodide (103 mg, 0.62 mmol) in dimethylacetamide (2 ml) at 95 °C for 4 hours under argon yielded 2-{3-[(7-{3-[cyclobutyl(2-

hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}-*N*-(2,3-difluorophenyl)acetamide (97 mg, 56 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.92 (s, 1H), 8.27 (s, 1H), 7.74 (m, 1H), 7.29 (s, 1H), 7.15-7.20 (m, 2H), 6.83 (s, 1H), 4.30 (m, 2H), 3.98 (s, 3H), 3.98 (m, 3H), 3.68-3.80 (m, 2H), 3.20-3.30 (m, 2H), 3.15 (m, 2H), 2.30 (m, 2H), 2.22 (m, 4H), 1.65-1.82 (m, 2H) :

MS (+ve ESI) : 582.2 $(M+H)^+$.

b) An analogous reaction to that described in example 6c, but starting with 2-{3-[(7-{3-[cyclobutyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}-*N*-(2,3-difluorophenyl)acetamide (668 mg, 1.15 mmol) yielded di-*tert*-butyl 2-{cyclobutyl[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate (450 mg, 51 % yield) :

^{1}H-NMR (DMSO d_6) : 8.44 (s, 1H), 7.98 (s, 1H), 7.70 (m, 1H), 7.18 (m, 3H), 6.83 (s, 1H), 4.15 (t, 2H), 3.90 (s, 3H), 3.85 (m, 4H), 3.15 (m, 1H), 2.62 (m, 4H), 1.90 (m, 4H), 1.75 (m, 2H), 1.53 (m, 2H), 1.39 (s, 18H) :

MS (+ve ESI) : 774.8 $(M+H)^+$.

Example 23 - Preparation of compound 23 in table 1 - 2-{cyclopentyl[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate

An analogous reaction to that described in example 1, but starting with di-*tert*-butyl 2-{cyclopentyl[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate (360 mg, 0.46 mmol) yielded compound 23 in table 1 (330 mg, 95 % yield) :

^{1}H-NMR (DMSO d_6, AcOD) : 8.91 (s, 1H), 8.32 (s, 1H), 7.70 (m, 1H), 7.43 (s, 1H), 7.20 (m, 2H), 6.82 (s, 1H), 4.31 (m, 4H), 4.00 (s, 3H), 3.94 (s, 2H), 3.80 (m, 1H), 3.48 (m, 2H), 3.36 (m, 2H), 2.33 (m, 2H), 2.08 (m, 2H), 1.75 (m, 4H), 1.58 (m, 2H) :

MS (+ve ESI) : 676.5 $(M+H)^+$.

di-*tert*-butyl 2-{cyclopentyl[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate used as starting material was obtained as follows :

a) An analogous reaction to that described in example 6b, but starting with 2-(cyclopentylamino)ethanol (129 mg, 1 mmol – prepared according to D.F. Morrow *et al. J. Med. Chem.* **1973**, *16*, 736-9.) yielded 2-{3-[(7-{3-[cyclopentyl(2-

hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}-*N*-(2,3-difluorophenyl)acetamide (86 mg, 48 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.93 (s, 1H), 8.28 (s, 1H), 7.73 (m, 1H), 7.30 (s, 1H), 7.14 (m, 2H), 6.83 (s, 1H), 4.29 (m, 2H), 3.98 (s, 3H), 3.93 (s, 2H), 3.78 (m, 3H), 3.37 (m, 2H), 3.26 (m, 2H), 2.30 (m, 2H), 2.09 (m, 2H), 1.74 (m, 4H), 1.72 (m, 2H) :

MS (+ve ESI) : 596.2 $(M+H)^+$.

b) An analogous reaction to that described in example 6c, but starting with 2-{3-[(7-{3-[cyclopentyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}-*N*-(2,3-difluorophenyl)acetamide (654 mg, 1.1 mmol) yielded di-*tert*-butyl 2-{cyclopentyl[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate (364 mg, 42 % yield) :

^{1}H-NMR (DMSO d_6) : 8.44 (s, 1H), 7.99 (s, 1H), 7.70 (m, 1H), 7.18 (m, 3H), 6.83 (s, 1H), 4.15 (m, 2H), 3.90 (s, 3H), 3.83 (m, 4H), 3.07 (m, 1H), 2.68 (m, 4H), 1.90 (m, 2H), 1.72 (m, 2H), 1.55 (m, 2H), 1.48 (m, 2H), 1.35 (m, 20H) :

MS (+ve ESI) : 789.0 $(M+H)^+$.

Example 24 - Preparation of compound 24 in table 1 - 2-{cyclopropyl[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate

Hydrochloric acid (1.05 ml of a 4.0 N solution in dioxane, 4.2 mmol) was added to a stirred suspension of di-*tert*-butyl 2-{cyclopropyl[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate (519 mg, 0.7 mmol) in dichloromethane (15 ml) and dioxane (30 ml) and the reaction stirred for 7 hours at 45 °C. The precipitate was recovered by suction filtration, the residue taken up in dichloromethane / methanol (8:2) and the solid material removed by filtration. The organic filtrate was evaporated *in vacuo* and the residue triturated with diethyl ether to yield compound 24 in table 1 (430 mg, 88 % yield) :

^{1}H-NMR (DMSO d_6, ACOH) : 8.91 (s, 1H), 8.32 (s, 1H), 7.64 (m, 1H), 7.39 (m, 3H), 6.90 (m, 1H), 6.80 (s, 1H), 4.32 (m, 4H), 4.00 (s, 3H), 3.87 (s, 2H), 3.57 (m, 2H), 3.48 (m, 2H), 2.95 (m, 1H), 2.40 (m, 2H), 1.18 (m, 2H), 0.92 (m, 2H) :

MS (+ve ESI) : 630.4 $(M+H)^+$.

di-*tert*-butyl 2-{cyclopropyl[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate used as starting material was obtained as follows :

a) Di-*tert*-butyl-diethylphosphoramidite (523 µl, 2.1 mmol) was added within 5 minutes to a solution of 2-{3-[(7-{3-[cyclopropyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}-*N*-(3-fluorophenyl)acetamide (793 mg, 1.4 mmol) in dimethylformamide (8 ml) in the presence of tetrazole (245 mg, 3.5 mmol) at ambient temperature under argon and the mixture was stirred for 1.5 hours.
The solution was cooled to 5 °C, cumene hydroperoxide (426 mg, 2.8 mmol) was slowly added, and the mixture stirred at 50 °C for 1 hour and at ambient temperature for a further 1 hour. The mixture was cooled to 5 °C and triethyl phosphite (415 mg, 2.5 mmol) was added and the reaction stirred at ambient temperature for 1 hour. The solution was diluted with water, extracted with ethyl acetate and the organic phase was separated, dried and concentrated. The resultant oil was purified by chromatography on silica gel, eluting with dichloromethane / methanol (98:2) to dichloromethane / methanol / ammonia (7.0 N) (95:5:1), to give di-*tert*-butyl 2-{cyclopropyl[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate as an off-white solid (630 mg, 59 % yield) :
^{1}H-NMR (DMSO d_6, TFA) : 8.97 (s, 1H), 8.32 (s, 1H), 7.65 (d, 1H), 7.35 (m, 3H), 6.86 (m, 2H), 4.33 (m, 4H), 4.03 (s, 3H), 3.87 (s, 2H), 3.66 (m, 2H), 3.53 (m, 2H), 3.00 (m, 1H), 2.38 (m, 2H), 1.45 (s, 18H), 1.07 (m, 2H), 0.96 (m, 2H) :
MS (+ve ESI) : 759.7 $(M+H)^+$.

Example 25 - Preparation of compound 25 in table 1 - 2-{(cyclopropylmethyl)[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate

An analogous reaction to that described in example 1, but starting with di-*tert*-butyl 2-{(cyclopropylmethyl)[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate (725 mg, 0.94 mmol) yielded compound 25 in table 1 (661 mg, 90 % yield) :
^{1}H-NMR (DMSO d_6, TFA) : 8.95 (s, 1H), 8.32 (s, 1H), 7.74 (m, 1H), 7.39 (s, 1H), 7.21 (m, 2H), 6.84 (s, 1H), 4.32 (t, 2H), 4.28 (m, 2H), 4.01 (s, 3H), 3.95 (s, 2H), 3.56 (br s, 2H), 3.46 (t, 2H), 3.19 (d, 2H), 2.32 (m, 2H), 1.18 (m, 1H), 0.68 (m, 2H), 0.47 (m, 2H) :

MS (+ve ESI) : 662.4 $(M+H)^+$.

di-*tert*-butyl 2-{(cyclopropylmethyl)[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl] amino}ethyl phosphate used as starting material was obtained as follows :

a) Ethylchloroformate (4.2 ml, 37 mmol) was added to a stirred solution of cyclopropylmethylamine (3.00 ml, 34.6 mmol) and triethylamine (7 ml) in dichloromethane (35 ml) at 0 °C over 30 minutes. The reaction was stirred at ambient temperature for 2 hours, water (20 ml) was added to the mixture, and the pH adjusted to 3 by addition of 2.0 N hydrochloric acid. The organic phase was separated, dried and concentrated *in vacuo* to yield ethyl (cyclopropylmethyl) carbamate (5.9 g, 100 % yield) :

^{1}H-NMR ($CDCl_3$) : 7.24 (br s, 1H), 3.24 (m, 2H), 1.43 (t, 3H), 1.04 (m, 1H), 0.59 (m, 2H), 0.29 (m, 2H) :

MS (+ve ESI) : 172 $(M+H)^+$.

b) A solution of ethyl (cyclopropylmethyl) carbamate (5.90 g, 34.6 mmol) in tetrahydrofuran (30 ml) was added at ambient temperature to a solution of diborane (130 ml of a 1.0 N solution in tetrahydrofuran, 130 mmol) and chlorotrimethylsilane (34 ml, 268 mmol) and the mixture stirred at ambient temperature for 48 hours. Methanol (20 ml) was added and the reaction stirred for 30 minutes at ambient temperature. Dichloromethane (25 ml)was added, followed by hydrochloric acid (4 ml of a 6.0 N solution, 24 mmol) and the reaction was stirred at ambient temperature for 30 minutes. Methanolic ammonia (7.0 N) was added, the white solid was collected by suction filtration and the organic filtrate was evaporated *in vacuo*. Purification by chromatography on silica gel, eluting with dichloromethane to dichloromethane / methanol (95:5) to dichloromethane / methanol / ammonia (7.0 N) (90:9:1), yielded 2-((cyclopropylmethyl)amino)ethanol as a pale yellow liquid (2.99 g, 75 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 3.66 (t, 2H), 3.02 (t, 2H), 2.84 (d, 2H), 1.06 (m, 1H), 0.58 (m, 2H), 0.35 (m, 2H).

c) An analogous reaction to that described in example 6b, but starting with 2-(cyclopropylmethyl)amino)ethanol (115 mg, 1 mmol) yielded 2-{3-[(7-{3-[(cyclopropylmethyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}-*N*-(2,3-difluorophenyl)acetamide (6 mg, 3 % yield) :

^{1}H-NMR (DMSO d_6) : 10.23 (s, 1H), 10.16 (s, 1H), 8.44 (s, 1H), 7.98 (s, 1H), 7.72 (m, 1H), 7.18 (m, 2H), 7.14 (s, 1H), 6.84 (s, 1H), 4.32 (s, 1H), 4.18 (t, 2H), 3.93 (s, 3H), 3.85 (s, 2H),

3.45 (m, 2H), 2.69 (t, 2H), 2.58 (t, 2H), 2.35 (d, 2H), 1.90 (m, 2H), 0.83 (m, 1H), 0.41 (m, 2H), 0.08 (m, 2H) :

MS (+ve ESI) : 582.2 $(M+H)^+$.

d) An analogous reaction to that described in example 6c, but starting with 2-{3-[(7-{3-[(cyclopropylmethyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}-*N*-(2,3-difluorophenyl)acetamide (673 mg, 1.16 mmol) yielded di-*tert*-butyl 2-{(cyclopropylmethyl)[3-({4-[(5-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate (110 mg, 12 % yield) :

^{1}H-NMR (DMSO d_6) : 10.23 (s, 1H), 10.15 (s, 1H), 8.44 (s, 1H), 7.98 (s, 1H), 7.72 (t, 1H), 7.19 (m, 2H), 7.13 (s, 1H), 6.83 (s, 1H), 4.17 (t, 2H), 3.93 (s, 3H), 3.88 (q, 2H), 3.85 (s, 2H), 2.76 (t, 2H), 2.72 (t, 2H), 2.38 (d, 2H), 1.91 (m, 2H), 1.37 (s, 18H), 0.83 (m, 1H), 0.42 (m, 2H), 0.09 (m, 2H) :

MS (+ve ESI) : 774.7 $(M+H)^+$.

Example 26 - Preparation of compound 26 in table 1 - 2-{cyclobutyl[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate

An analogous reaction to that described in example 1, but starting with di-*tert*-butyl 2-{cyclobutyl[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate (416 mg, 0.55 mmol) yielded compound 26 in table 1 (455 mg, 100 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.94 (s, 1H), 8.31 (s, 1H), 7.65 (d, 1H), 7.38 (m, 2H), 7.36 (s, 1H), 6.90 (m, 1H), 6.83 (s, 1H), 4.30 (t, 2H), 4.22 (m, 2H), 4.01 (s, 3H), 3.94 (m, 1H), 3.86 (s, 2H), 3.37 (s, 2H), 3.27 (br s, 2H), 2.35 (t, 2H), 2.26 (m, 4H), 1.77 (m, 1H), 1.68 (m, 1H) :

MS (+ve ESI) : 644.2 $(M+H)^+$.

di-*tert*-butyl 2-{cyclobutyl[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate used as starting material was obtained as follows :

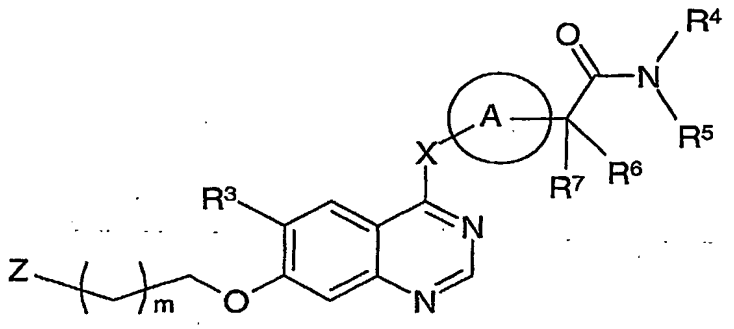
a) An analogous reaction to that described in example 5a, but starting with 2-(cyclobutylamino)ethanol (178 mg, 1.55 mmol) yielded 2-{3-[(7-{3-[cyclobutyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}-*N*-(3-fluorophenyl)acetamide (42 mg, 24 % yield) :

^{1}H-NMR (DMSO d_6, TFA) : 8.96 (s, 1H), 8.29 (s, 1H), 7.64 (d, 1H), 7.36 (m, 2H), 7.34 (s, 1H), 6.90 (t, 1H), 6.83 (s, 1H), 4.29 (t, 2H), 4.00 (s, 3H), 3.94 (m, 1H), 3.85 (s, 2H), 3.75 (m, 2H), 3.25 (m, 2H), 3.17 (m, 2H), 2.08-2.39 (m, 6H), 1.76 (m, 1H), 1.69 (m, 1H) :
MS (+ve ESI) : 564.2 $(M+H)^+$.

b) An analogous reaction to that described in example 5b, but starting with 2-{3-[(7-{3-[cyclobutyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-5-yl}-*N*-(3-fluorophenyl)acetamide (474 mg, 0.84 mmol) yielded di-*tert*-butyl 2-{cyclobutyl[3-({4-[(5-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-3-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate (109 mg, 17 % yield) :
^{1}H-NMR (DMSO d_6) : 10.46 (s, 1H), 10.16 (s, 1H), 8.44 (s, 1H), 7.98 (s, 1H), 7.62 (d, 1H), 7.34 (m, 1H), 7.33 (s, 1H), 7.13 (s, 1H), 6.89 (t, 1H), 6.82 (s, 1H), 4.15 (t, 2H), 3.93 (s, 3H), 3.84 (q, 2H), 3.76 (s, 2H), 3.16 (m, 1H), 2.64 (t, 2H), 2.59 (t, 2H), 1.96 (m, 2H), 1.88 (m, 2H), 1.77 (m, 2H), 1.55 (m, 2H), 1.38 (s, 18H) :
MS (+ve ESI) : 756.7 $(M+H)^+$.

CLAIMS

1. A compound of formula (I):



formula (I)

wherein A is 5-membered heteroaryl containing a nitrogen atom and optionally containing one or two further nitrogen atoms;

X is O, S, S(O), $S(O)_2$ or NR^{14};

m is 0, 1, 2 or 3;

Z is a group selected from $-NR^1R^2$, phosphonooxy, C_{3-6}cycloalkyl (substituted by phosphonooxy or C_{1-4}alkyl (substituted by phosphonooxy)) and a 4- to 7-membered ring linked via a carbon atom containing a nitrogen atom and optionally containing a further nitrogen atom, which ring may be saturated, partially saturated or unsaturated wherein the ring is substituted on carbon or nitrogen by phosphonooxy or C_{1-4}alkyl (substituted by phosphonooxy) and wherein the ring is optionally further substituted on carbon or nitrogen by 1, 2 or 3 halo or C_{1-4}alkyl groups;

R^1 is $-COR^8$, $-CONR^8R^9$ or C_{1-6}alkyl (substituted by phosphonooxy and optionally further substituted by 1 or 2 halo or methoxy groups);

R^2 is hydrogen, $-COR^{10}$, $-CONR^{10}R^{11}$, C_{1-6}alkyl (optionally substituted by 1, 2 or 3 halo or C_{1-4}alkoxy groups or $-S(O)_pR^{11}$ (where p is 0, 1 or 2) or phosphonooxy), C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl and C_{3-6}cycloalkylC_{1-4}alkyl;

or R^1 and R^2 together with the nitrogen to which they are attached form a 4- to 7- membered ring optionally containing a further nitrogen atom which may be saturated, partially saturated or unsaturated wherein the ring is substituted on carbon or nitrogen by a group selected from phosphonooxy and C_{1-4}alkyl (substituted by phosphonooxy or $-NR^8R^9$) and where the ring is optionally further substituted on carbon or nitrogen by 1, 2 or 3 halo or C_{1-4}alkyl groups;

R^3 is hydrogen, halo, cyano, nitro, C_{1-6}alkoxy, C_{1-6}alkyl, $-OR^{12}$, $-CHR^{12}R^{13}$, $-OC(O)R^{12}$, $-C(O)R^{12}$, $-NR^{12}C(O)R^{13}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}SO_2R^{13}$ or $-NR^{12}R^{13}$;

R^4 is hydrogen or a group selected from C_{1-4}alkyl, heteroaryl, heteroarylC_{1-4}alkyl, aryl and arylC_{1-4}alkyl where the group is optionally substituted by 1, 2 or 3 substitutents selected from halo, methyl, ethyl, cyclopropyl and ethynyl;

R^5 is selected from hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{3-6}cycloalkyl and C_{3-6}cycloalkylC_{1-4}alkyl;

R^6 and R^7 are independently hydrogen, halo, C_{1-4}alkyl, C_{3-6}cycloalkyl, hydroxy and C_{1-4}alkoxy;

R^8 is C_{1-4}alkyl substituted by phosphonooxy and optionally further substituted by 1 or 2 halo or methoxy groups;

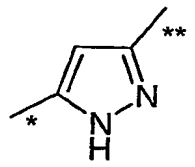
R^9 is hydrogen or C_{1-4}alkyl;

R^{10} is hydrogen or C_{1-4}alkyl (optionally substituted by halo, C_{1-4}alkoxy, $S(O)_q$ (where q is 0, 1 or 2) or phosphonoxy);

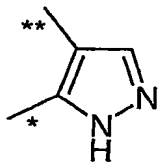
R^{11}, R^{12}, R^{13} and R^{14} are independently hydrogen, C_{1-4}alkyl or heterocyclyl;

or a pharmaceutically acceptable salt thereof.

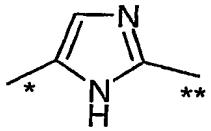
2. A compound according to claim 1 wherein A is a group of formula (a), (b), (c), (d) or (e):



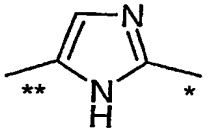
(a)



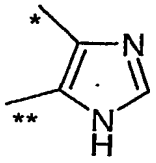
(b)



(c)



(d)



(e)

where * is the point of attachment to the X group of formula (I) and ** is the point of attachment to the (CR^6R^7) group of formula (I).

3. A compound according to claim 2 wherein A is a group of formula (a) as defined in claim 2.

4. A compounds according to any one of claims 1, 2 or 3 wherein X is NH.

5. A compound according to any one of the preceding claims wherein Z is $-NR^1R^2$.

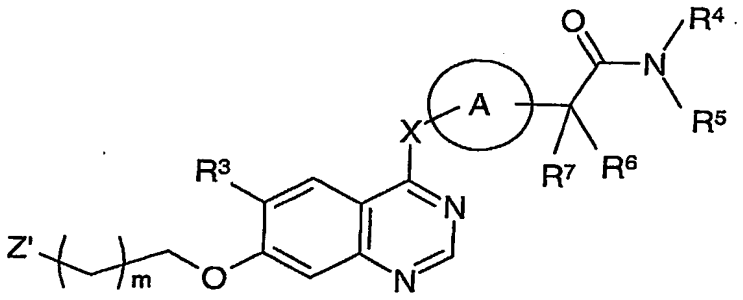
6. A pharmaceutical composition comprising a compound according to any one of the preceding claims in association with a pharmaceutically acceptable diluent or carrier.

7. Use of a compound according to any one of claims 1 to 5 in therapy.

8. Use of a compound according to any one of claims 1 to 5 in the preparation of a medicament for the treatment of a disease where the inhibition of one or more Aurora kinase is beneficial.

9. Use according to claim 8 wherein Aurora kinase is Aurora-A kinase or Aurora-B kinase.

10. A process for the preparation of a compound according to claim 1 comprising converting a compound of formula (II) into a compound of formula (I) by phosphorylation of an appropriate hydroxy group:



formula (II)

where A, X, m, R^2, R^3, R^4, R^5, R^6, R^7 and R^9 are as defined for claim 1;

Z' is a group selected from $-NR^{1'}R^2$, hydroxy, C_{3-6}cycloalkyl (substituted by hydroxy or C_{1-4}alkyl (substituted by hydroxy)) and a 4- to 7-membered ring linked via a carbon atom

containing a nitrogen atom and optionally containing a further nitrogen atom, which ring may be saturated, partially saturated or unsaturated wherein the ring is substituted on carbon or nitrogen by hydroxy or C_{1-4}alkyl (substituted by hydroxy) and wherein the ring is optionally further substituted on carbon or nitrogen by 1, 2 or 3 halo or C_{1-4}alkyl groups;

$R^{1'}$ is $-COR^{8'}$, $-CONR^{8'}R^9$ or C_{1-6}alkyl (substituted by hydroxy and optionally further substituted by 1 or 2 halo or methoxy groups); or $R^{1'}$ and R^2 together with the nitrogen to which they are attached form a 4- to 7- membered ring optionally containing a further nitrogen atom which may be saturated, partially saturated or unsaturated wherein the ring is substituted on carbon or nitrogen by a group selected from hydroxy and C_{1-4}alkyl (substituted by hydroxy or $-NR^{8'}R^9$) and where the ring is optionally further substituted on carbon or nitrogen by 1, 2 or 3 halo or C_{1-4}alkyl groups; and

$R^{8'}$ is C_{1-4}alkyl substituted by hydroxy and optionally further substituted by 1 or 2 halo or methoxy groups:

and thereafter if necessary:

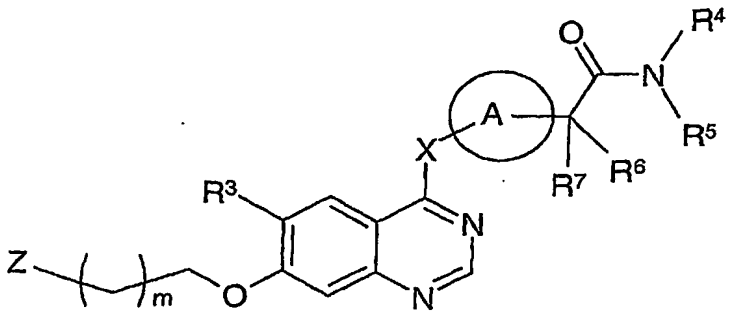
i) converting a compound of the formula (I) into another compound of the formula (I);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt.

ABSTRACT

Quinazoline derivatives of formula (I):



wherein A is 5-membered heteroaryl containing a nitrogen atom and one or two further nitrogen atoms; compositions containing them, processes for their preparation and their use in therapy.

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